



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL
SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: March 15, 2017

SUBJECT: **Difenoconazole:** Human Health Risk Assessment for Proposed New Foliar Uses on Cotton, Rice and Wild Rice.

PC Code: 128847
Decision No.: 513780

Petition No.: 6F8445
Risk Assessment Type: Single Chemical Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D432211
Registration Nos.: 100-739 (technical product),
100-1262, 100-1312, 100-1313, 100-1476 and 100-1554
Regulatory Action: Section 3 Registration
Case No.: 7014
CAS No.: 119446-68-3
40 CFR: §180.475

FROM: Bonnie Cropp-Kohlligian, Environmental Scientist
Thurston G. Morton, Senior Chemist
Abdallah Khasawinah, Ph.D., Toxicologist
Risk Assessment Branch IV
Health Effects Division (7509P)

Bonnie Cropp-Kohlligian
Thurston G. Morton
Abdallah Khasawinah

THROUGH: Wade Britton, MPH, Acting Branch Chief
Risk Assessment Branch IV
Health Effects Division (7509P)

Wade Britton

TO: Lindsay Roe/Tony Kish (RM 22)
Fungicide Branch
Registration Division (7505P)

The Registration Division (RD) has requested an assessment of human health risk to support the proposed new foliar uses of difenoconazole on cotton, rice and wild rice and the establishment of related tolerances for residues of difenoconazole. This document provides the Health Effects Division (HED) human health risk assessment for the proposed new uses of difenoconazole.

Table of Contents

1.0 EXECUTIVE SUMMARY	4
2.0 HED RECOMMENDATIONS.....	7
2.1 Data Deficiencies.....	7
2.2 Tolerance Considerations	7
2.2.1 Enforcement Analytical Method	7
2.2.2 Analytical Reference Standard.....	8
2.2.3 Recommended Tolerances.....	8
2.2.4 Revisions to Petitioned-For Tolerances	9
2.2.5 International Harmonization.....	9
2.3 Label Recommendations.....	9
3.0 INGREDIENT PROFILE	9
3.1 Chemical Identity	9
3.2 Physical/Chemical Characteristics.....	10
3.3 Pesticide Use Pattern	10
3.4 Anticipated Exposure Pathways.....	14
3.5 Considerations of Environmental Justice	14
4.0 HAZARD CHARACTERIZATION AND DOSE-RESPONSE ASSESSMENT.....	15
4.1 Toxicology Studies Available for Analysis	15
4.2 Absorption, Distribution, Metabolism and Excretion (ADME).....	15
4.3 Toxicological Effects.....	16
4.4 Safety Factor for Infants and Children (FQPA Safety Factor).....	17
4.4.1 Completeness of the Toxicology Database.....	17
4.4.2 Evidence of Neurotoxicity	17
4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal	17
4.4.4 Residual Uncertainty in the Exposure Database.....	18
4.5 Toxicity Endpoint and Point of Departure Selections.....	18
4.5.1 Dose-Response Assessment	18
4.5.2 Recommendations for Combining Exposure Routes for Risk Assessment	19
4.5.3 Cancer Classification and Risk Assessment Recommendations.....	19
4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Risk Assessment	19
5.0 DIETARY EXPOSURE AND RISK ASSESSMENT	21
5.1 Metabolite/Degradate Residue Profile.....	21

5.1.1	Summary of Plant and Animal Metabolism Studies	21
5.1.2	Summary of Environmental Degradation	22
5.1.3	Comparison of Metabolic Pathways.....	22
5.1.4	Residues of Concern Summary and Rationale.....	22
5.2	Food Residue Profile	23
5.2.1	Residues in Crops.....	23
5.3	Water Residue Profile	25
5.3.1	Estimated Drinking Water Concentrations.....	25
5.4	Dietary Risk Assessment.....	26
5.4.1	Description of Residue Data Used in Dietary Assessment	26
5.4.2	Percent Crop Treated Used in Dietary Assessment.....	27
5.4.3	Acute Dietary Risk Assessment	27
5.4.4	Chronic Dietary Risk Assessment	27
5.4.5	Summary Findings of Separate Dietary Assessment for Triazole Metabolites.	28
6.0	RESIDENTIAL (NON-OCCUPATIONAL) EXPOSURE/RISK CHARACTERIZATION	29
6.1	Non-Occupational Residential Bystander Postapplication Inhalation Exposure and Risk Estimates.....	31
6.2	Non-Occupational Spray Drift Exposure and Risk Estimates	32
7.0	AGGREGATE EXPOSURE/RISK CHARACTERIZATION.....	32
7.1	Acute & Chronic Aggregate Risk.....	32
7.2	Short-Term Aggregate Risk	32
7.3	Intermediate-Term Aggregate Risk.....	33
7.4	Summary Findings of Separate Aggregate Assessment for Triazole Metabolites...	33
8.0	CUMULATIVE EXPOSURE/RISK CHARACTERIZATION	33
9.0	OCCUPATIONAL EXPOSURE/RISK CHARACTERIZATION	34
9.1	Occupational Handler Exposure and Risk Estimates	34
9.2	Occupational Post-Application Exposure and Risk Estimates	35
9.2.1	Restricted Entry Interval	36
10.	REFERENCES.....	37
	APPENDIX A. TOXICOLOGY DATA SUMMARY	38
	APPENDIX B. PHYSICAL/CHEMICAL PROPERTIES	47
	APPENDIX C. STUDIES REVIEWED FOR ETHICAL CONDUCT.....	48

1.0 EXECUTIVE SUMMARY

Difenoconazole is a broad spectrum fungicide belonging to the triazole group of fungicides. It acts by blocking demethylation during sterol biosynthesis which, in turn, disrupts membrane synthesis. Syngenta Crop Protection, LLC (hereafter referred to as Syngenta or petitioner) is proposing new foliar uses of difenoconazole on cotton, rice and wild rice.

This document addresses the exposures and risks associated with currently registered and proposed new uses of difenoconazole only. It also assesses potential enhanced sensitivity of infants and children from dietary and/or residential exposure as required under the Food Quality Protection Act (FQPA) of 1996.

Use Profile

Difenoconazole is currently registered in the U.S. for use as a seed treatment on a number of cereal grain crops (barley, oats, rye, sweet corn, triticale and wheat), canola, cotton, and potato seed pieces and for foliar applications on numerous crops, landscape ornamentals and golf course turf and for post-harvest uses on members of tuberous and corm vegetables subgroup 1C and pome fruit group 11-10. It is available as emulsifiable concentrate (EC), soluble concentrate (SC), emulsion [oil] in water, flowable suspension, and ready-to-use formulations. As a seed treatment, it is applied with commercial grade seed treatment equipment. As a foliar treatment, it is applied by commercial applicators using aerial and ground application methods and equipment. It is applied to ornamentals by residential applicators using hand held sprayers.

Syngenta has submitted directions for foliar uses on cotton, rice and wild rice for the 2.08 lb ai/gal EC formulation of difenoconazole (Inspire™ Fungicide; EPA Reg. No. 100-1262). In addition, Syngenta is proposing to add some or all of the proposed uses to the following multiple active ingredient (MAI) products: a 2.08 lb ai/gal MAI EC formulation with propiconazole (Inspire® XT Fungicide; EPA Reg. No. 100-1312); a 1.05 lb ai/gal MAI SC formulation with azoxystrobin (Quadris Top® Fungicide; EPA Reg. No. 100-1313); a 0.97 lb ai/gal MAI EC formulation with benzovindiflupyr (Aprovia® Top Fungicide; EPA Reg. No. 100-1476); and a 1.88 lb ai/gal MAI SC formulation with azoxystrobin (Quadris Top® SBX Fungicide; EPA Reg. No. 100-1554). Note: Active ingredients other than difenoconazole are not addressed herein.

The proposed cotton use is for multiple foliar applications at up to 0.115 lb ai/A/application for a maximum seasonal rate of 0.34 lb ai/A/year, with a 14-day minimum retreatment interval (RTI) and a 45-day preharvest interval (PHI). The proposed rice and wild rice uses are for multiple foliar applications during flooding at up to 0.123 lb ai/A/application for a maximum seasonal rate of 0.246 lb ai/A/year, with a 14-day minimum RTI and 28-day PHI. Permanent flood waters may not be released until 7-days after application to rice or wild rice. The proposed rice and wild rice uses include restrictions to prevent residue exposure for irrigation and aquaculture.

Note: Syngenta is not proposing the use of the 0.97 lb ai/gal MAI EC formulation with benzovindiflupyr (Aprovia® Top Fungicide; EPA Reg. No. 100-1476) on rice or wild rice because there are no currently established tolerances for residues of benzovindiflupyr in/on rice or wild rice. Syngenta is not proposing the use of the 2.08 lb ai/gal MAI EC formulation with

propiconazole (Inspire® XT Fungicide; EPA Reg. No. 100-1312) on cotton because there is no currently established tolerance for residues for propiconazole in/on cotton commodities. Further, the proposed use of the 2.08 lb ai/gal MAI EC formulation with propiconazole (Inspire® XT Fungicide; EPA Reg. No. 100-1312) on wild rice is restricted to Minnesota (MN) because the currently established tolerance for residues of propiconazole in/on wild rice is a tolerance with regional restrictions.

Toxicological Effects

The toxicology database for difenoconazole is complete for evaluating and characterizing toxicity and selecting endpoints for purposes of this risk assessment. Subchronic and chronic toxicity studies with difenoconazole in mice and rats showed decreased body weights and effects on the liver (e.g. hepatocellular hypertrophy, liver necrosis, fatty changes in the liver). Acute and subchronic neurotoxicity studies showed evidence of mild neurotoxic effects; however, the observed effects were transient and showed in one sex (males as reduced fore-limb grip strength with no histologic findings) and the selected endpoints of toxicity for risk assessment are protective of any potential neurotoxicity. The available developmental and reproduction toxicity studies indicated no increased susceptibility of rats from *in utero* or postnatal exposure to difenoconazole. In rabbits there was qualitative susceptibility since the developmental effects were more severe than the maternal effects seen at the same dose; however, the toxicological point of departure (POD) selected to assess acute dietary exposures is protective from these effects. In an immunotoxicity study in mice, difenoconazole produced immunotoxicity at doses that caused systemic toxicity. No evidence of carcinogenicity was seen in the chronic/cancer rat study. Evidence for carcinogenicity was seen in mice as induction of liver tumors at doses which were considered to be excessively high for carcinogenicity testing. Difenoconazole has been classified as “Suggestive Evidence of Carcinogenic Potential” with risk quantified using a non-linear (Margin of Exposure) approach (TXR 0054532). The cancer classification is based on excessive toxicity observed at the two highest doses, the absence of tumors at the lower doses and the absence of genotoxic effects. The FQPA Safety Factor is reduced to 1X.

Difenoconazole exhibits low acute toxicity by the oral, dermal and inhalation routes of exposure. It is not an eye or skin irritant and is not a sensitizer.

Dose Response Assessment

Acute and chronic toxicological PODs were selected for dietary and drinking water exposures for the assessment of proposed new uses of difenoconazole. An acute POD for all populations was selected from an acute neurotoxicity study in rats based on reduced grip strength. A chronic POD was selected from a chronic/carcinogenicity study in rats based on body weight effects. Short- and intermediate-term incidental oral, dermal and inhalation PODs were selected from an oral rat reproduction study based on decreased body weight effects in pups and parental animals. A dermal absorption factor is applied when dermal exposure endpoints are selected from oral toxicity studies. A dermal absorption factor of 6%, based on triple pack data, was used for the dermal exposure assessment. Inhalation toxicity is assumed to be equivalent to oral toxicity. An uncertainty factor of 100X was applied to endpoints selected for all exposures routes (10X for interspecies extrapolation, 10X for intraspecies variation, 1X FQPA safety factor (SF)).

Exposure/Risk Assessment and Risk Characterization

Unrefined acute and refined chronic dietary and drinking water risk assessments for difenoconazole conclude that dietary and drinking water exposure estimates are below HED's level of concern for the general population and all population subgroups. The assessments included the following updates to the previous dietary risk assessment: (1) new drinking water estimates provided by the Environmental Fate and Effects Division (EFED); and (2) new percent crop treated estimates provided by the Biological and Economic Analysis Division (BEAD) which were incorporated into the refined chronic dietary assessment.

At the 95th percentile, the acute dietary exposure to the general U.S. population is 17% of the acute population adjusted dose (aPAD); the highest exposed subgroup (All Infants < 1 yr) is 53% of the aPAD. The chronic dietary exposure to the general U.S. population is 18% of the chronic population adjusted dose (cPAD), and the most highly exposed subgroup (All Infants < 1 yr) is 50% of the cPAD.

A new residential assessment was not performed since there are no proposed new residential uses associated with this new petition. The currently registered outdoor and indoor residential exposure scenarios have been previously assessed for all difenoconazole uses based on the Revised Residential SOPs (2012); no risk estimates of concern were identified (D421188, I. Nieves, 2/24/2015). Previously assessed residential exposure risk estimates were combined with current dietary exposure estimates for the aggregate risk assessment. Aggregate risk estimates were not of concern. Risk estimates for occupational handler and post-application exposure scenarios for all proposed uses have also been previously assessed at similar use rates, amounts used and area treated (D421188, I. Nieves, 2/24/2015). None of the existing or proposed new uses were of concern at maximum use rates with label required PPE (personal protective equipment; *i.e.*, long shirt, long pants, shoes, socks and gloves).

Aggregate Assessment of Free Triazole & its Conjugates

Application of triazole-containing pesticides, such as difenoconazole, also result in exposure to free triazole and its conjugates which are considered toxicologically different from difenoconazole and are assessed separately from the parent compound. The previous aggregate human health risk assessment for free triazoles and its conjugates was updated and the aggregate estimates remain below HED's level of concern (D436745, T. Morton, 11/15/2016).

Use of Human Studies

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, listed in Appendix 2.0, have been determined to require a review of their ethical conduct. Some of these studies are also subject to review by the Human Studies Review Board. All of the studies used have received the appropriate review.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," <http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf>.

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development, as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

2.0 HED RECOMMENDATIONS

HED recommends in favor of the proposed new foliar uses of difenoconazole on cotton, rice and wild rice provided the petitioner complies with the tolerance recommendations (*see* sections 2.2.3 and 2.2.4).

2.1 Data Deficiencies

None.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

An adequate enforcement method, gas chromatography with nitrogen-phosphorus detection (GC/NPD) method AG-575B, is available for the determination of residues of difenoconazole *per se* in/on plant commodities. An adequate enforcement method, GC/MSD method AG-676A, is also available for the determination of residues of difenoconazole *per se* in/on canola and barley commodities. A confirmatory method, GC/MSD method AG-676, is also available. The LOQs are 0.01-0.05 ppm.

2.2.2 Analytical Reference Standard

Analytical reference standards for difenoconazole and CGA-205375 are currently available in the EPA National Pesticide Standards Repository (NPSR) and have expiration dates of 2/28/2019 and 6/30/2017, respectively (email communication between T. Cole and B. Cropp-Kohlligian, 8/4/2016).

2.2.3 Recommended Tolerances

HED has examined the residue chemistry database for difenoconazole. The newly submitted cotton and rice field trial and processing data for difenoconazole are adequate to support the proposed uses on cotton, rice and wild rice. These data were generated with an adequate data-collection method and are supported by adequate storage stability data. There are no residue chemistry issues that would preclude granting the proposed new uses or establishment of the tolerances for residues of difenoconazole specified in Table 2.2.3.1 below.

In addition, with the establishment of a tolerance in/on cottonseed subgroup 20C the currently established tolerance for residues of difenoconazole in/on cotton, undelinted seed (0.05 ppm) for seed treatment use should be removed.

Tolerances for plant commodities are established under 40 CFR §180.475(a)(1), and are expressed in terms of difenoconazole only. The current tolerance expression is in accordance with current guidance (Knizner, 5/27/09). The tolerances proposed by Syngenta were in terms of difenoconazole only and are listed in Table 2.2.3.1 along with the tolerances recommended by HED and correct commodity definitions.

Table 2.2.3.1. Tolerance Summary for Difenoconazole.			
Commodity	Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Correct Commodity Definition Comments
Cottonseed subgroup 20C	0.40	0.40	<i>Cottonseed subgroup 20C</i> For new foliar use of difenoconazole. Cottonseed is the representative commodity for this crop subgroup.
Cotton, gin byproducts	Increase the currently established tolerance from 0.05 to 15	15	<i>Cotton gin byproducts</i>
Rice, grain	7.0	7.0 ¹	<i>Rice, grain</i>
Rice, Wild, grain	7.0	7.0	<i>Rice, wild, grain</i>
Cotton, undelinted seed	Remove the currently established at 0.05 ppm for seed treatment use of difenoconazole.	Remove	With the establishment of a tolerance in/on cottonseed subgroup 20C for foliar use of difenoconazole on cotton, this tolerance is no longer needed for seed treatment use of difenoconazole.

¹ In addition to supporting rice grain data conducted in the U.S. and reflecting the maximum proposed use rate, Syngenta also submitted non-domestic rice grain data conducted in China/India/Thailand and reflecting a use rate/pattern that is different (more applications, shorter RTI and shorter PHI) from that proposed for use in the U.S. HED notes that the petitioned-for/recommended tolerance for residues in/on rice, grain (7.0 ppm) would not be

adequate to cover residues of difenoconazole in/on rice, grain treated in accordance with the use rate/pattern reflected by the non-domestic data. However, Syngenta has confirmed (letter from Adora Clark of Syngenta to L. Roe/T. Kish dated 5/26/16) that the subject non-domestic rice grain data were not submitted in support of the tolerance in/on rice grain but were only provided as part of the rice processing study.

2.2.4 Revisions to Petitioned-For Tolerances

Section F of the petition should be revised to specify the correct commodity definitions for Cotton, gin byproducts; and Rice, Wild, grain which are, *Cotton gin byproducts; and Rice, wild, grain*, respectively.

2.2.5 International Harmonization

Codex maximum residue limits (MRLs) are not established for residues of difenoconazole in/on cottonseed subgroup 20C, rice or wild rice commodities. Mexico adopts U.S. tolerances and/or Codex MRLs for its export purposes. Canadian MRLs have been established for difenoconazole; however, no MRLs have been established for the requested crops with the exception of wild rice. Harmonization of the recommended U.S. tolerance level in/on rice, wild, grain (7.0 ppm) with the established Canadian MRL in/on wild rice (0.01 ppm) is not possible due to differences in good agriculture practices (GAP).

2.3 Label Recommendations

None.

3.0 INGREDIENT PROFILE

3.1 Chemical Identity

The chemical structure and nomenclature of difenoconazole, its regulated livestock metabolite CGA-205375, and the triazole metabolites are presented in Tables 3.1.1.

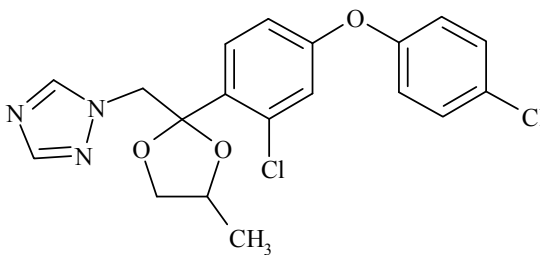
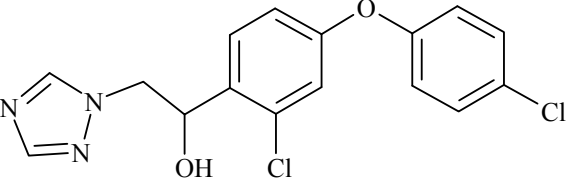
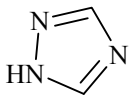
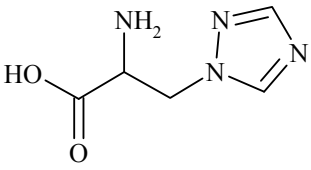
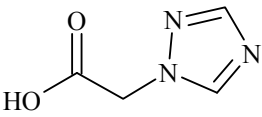
Table 3.1.1. Difenoconazole Nomenclature.	
Chemical structure of parent	 <p style="text-align: right;">mol. wt. 406.3</p>
Common name	Difenoconazole
Company experimental name	CGA-169374
IUPAC name	1-[2-[2-chloro-4-(4-chloro-phenoxy)-phenyl]-4-methyl-[1,3]dioxolan-2-ylmethyl]-1H-[1,2,4]triazole
CAS name	1-[[2-[2-chloro-4-(4-chlorophenoxy)phenyl]-4-methyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole

Table 3.1.1. Difenoconazole Nomenclature.	
CAS registry number	119446-68-3
Chemical structure of CGA-205375 livestock metabolite	 mol. wt. 349.2
Chemical structure of 1,2,4-Triazole (1,2,4-T)	
Chemical structure of Triazolyl alanine (TA)	
Chemical structure of Triazolyl acetic acid (TAA)	

3.2 Physical/Chemical Characteristics

The physicochemical properties of difenoconazole are reported in Appendix B.

3.3 Pesticide Use Pattern

Under revised Section B (dated 5/25/16; E-Sub# 11862) of the petition 6F8445, Syngenta has submitted directions for foliar uses of difenoconazole on cotton, rice and wild rice for the 2.08 lb ai/gal emulsifiable concentrate (EC) formulation of difenoconazole (Inspire™ Fungicide; EPA Reg. No. 100-1262). In addition, Syngenta is proposing to add some or all of the proposed uses to the following multiple active ingredient (MAI) products: a 2.08 lb ai/gal MAI EC formulation with propiconazole (Inspire® XT Fungicide; EPA Reg. No. 100-1312); a 1.05 lb ai/gal MAI suspension concentrate (SC) formulation with azoxystrobin (Quadris Top® Fungicide; EPA Reg. No. 100-1313); a 0.97 lb ai/gal MAI EC formulation with benzovindiflupyr (Aprovia® Top Fungicide; EPA Reg. No. 100-1476); and a 1.88 lb ai/gal MAI SC formulation with azoxystrobin (Quadris Top® SBX Fungicide; EPA Reg. No. 100-1554). In addition, Syngenta submitted revised draft labels (dated 5/25/16; E-Sub#s 11860, 11861, 11864, 11865 and 11866), which are substantially similar to Section B of the petition. The subject end-use products are identified in Table 3.3.1, and the use directions based on the revised draft labels are summarized in Table 3.3.2.

Table 3.3.1. Summary of End-Use Products and Crops Under Consideration.

Trade Name	EPA Reg. No.	ai Content	Formulation Type	Target Crops	Source of Use Directions
Inspire® Fungicide	100-1262	<u>Difenoconazole</u> 2.08 lb ai/gal (23.2%)	Emulsifiable concentrate (EC)	Cotton; rice; wild rice.	Revised Draft Label Dated 5/25/16 (E-Sub# 11861)
Inspire® XT Fungicide	100-1312	<u>Difenoconazole</u> 2.08 lb ai/gal (22.8%) <u>Propiconazole</u> 2.08 lb ai/gal (22.8%)	EC	Rice; wild rice (MN only).	Revised Draft Label Dated 5/25/16 (E-Sub# 11864)
Quadris Top® Fungicide	100-1313	<u>Difenoconazole</u> 1.05 lb ai/gal (11.4%) <u>Azoxystrobin</u> 1.67 lb ai/gal (18.2%)	Suspension concentrate (SC)	Cotton; rice; wild rice.	Revised Draft Label Dated 5/25/16 (E-Sub# 11865)
Aprovia® Top Fungicide	100-1476	<u>Difenoconazole</u> 0.97 lb ai/gal (11.25%) <u>Benzovindiflupyr</u> 0.65 lb ai/gal (7.50%)	EC	Cotton.	Revised Draft Label Dated 5/25/16 (E-Sub# 11860)
Quadris Top® SBX Fungicide	100-1554	<u>Difenoconazole</u> 1.88 lb ai/gal (19.8%) <u>Azoxystrobin</u> 1.88 lb ai/gal (19.8%)	SC	Cotton; Rice; and Wild Rice.	Revised Draft Label Dated 5/25/16 (E-Sub# 11866)

Table 3.3.2. Summary of Directions for Use of Difenoconazole.

Appl. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Max. Appl. Rate (lb ai/A)	Max. No. Appl. per Season	Max. Yearly Appl. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Cotton Note: Because there is no currently established tolerance for residues of propiconazole in/on cotton commodities, Syngenta is not proposing use of Inspire® XT Fungicide (EPA Reg. No. 100-1312) on cotton.						
Foliar, Broadcast, Ground (≥ 10 gal/A), aerial (≥ 5 gal/A) or chemigation (0.1-0.25 inches/A)	2.08 lb ai/gal EC [100-1262]	0.114	Not Specified (NS)	0.34	45	The minimum retreatment interval (RTI) is 14 days. Make no more than 2 sequential applications before alternating to another fungicide with a different mode of action.
	1.05 lb ai/gal MAI SC [100-1313]	0.115				Same as for 100-1262.
	0.97 lb ai/gal MAI EC [100-1476]	0.104	NS	0.20	45	Maximum use rate for all difenoconazole-containing products is 0.34 lb ai/A/yr. Otherwise, same as for 100-1262.
	1.88 lb ai/gal MAI SC [100-1554]	0.113	NS	0.34	45	Same as for 100-1262

Table 3.3.2. Summary of Directions for Use of Difenoconazole.

Appl. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Max. Appl. Rate (lb ai/A)	Max. No. Appl. per Season	Max. Yearly Appl. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Rice and Wild Rice Note: Because there are no currently established tolerances for residues of benzovindiflupyr in/on rice or wild rice, Syngenta is not proposing use of Aprovia® Top Fungicide (EPA Reg. No. 100-1476) on rice and wild rice. Because the currently established tolerance for residues of propiconazole in/on wild rice is a tolerance with regional registrations, the proposed use of Inspire® XT Fungicide (EPA Reg. No. 100-1312) on wild rice is restricted to MN.						
Foliar, Broadcast, Ground (≥ 10 gal/A) or aerial (≥ 5 gal/A)	2.08 lb ai/gal EC [100-1262]	0.122	NS	0.244	28	The minimum RTI is 14 days. For Rice: Apply when disease is less than 4 inches above water line usually between panicle differentiation (PD) +5days to PD +10 days or at initial sign of disease. For Wild Rice: Apply at both booting and heading. Applicators should use care in making applications near non-target aquatic habitats. Do not allow release of irrigation or flood water for at least 7 days after the last application. Do not treat fields used for aquaculture of fish or crustacean. Do not drain water from treated rice fields into ponds used for aquaculture of fish and crustacean. Do not drain from treated field to irrigate other crops.
Foliar, Broadcast, Ground (≥ 15 gal/A) or aerial (≥ 5 gal/A)	2.08 lb ai/gal MAI EC [100-1312]	0.122	NS	0.244	35	For use on wild rice in MN only. Do not apply to stubble or ratoon crop rice. Otherwise same as for 100-1262.
Foliar, Broadcast, Ground (≥ 10 gal/A) or aerial (≥ 5 gal/A)	1.05 lb ai/gal MAI SC [100-1313]	0.123	NS	0.246	28	Same as for 100-1262.
Foliar, Broadcast, Ground (≥ 10 gal/A) or aerial (≥ 5 gal/A)	1.88 lb a/gal MAI SC [100-1554]	0.122	NS	0.244	28	Same as for 100-1262.

PHI = preharvest interval.

3.4 Anticipated Exposure Pathways

The Registration Division has requested an assessment of human health risk to support the proposed new foliar uses of difenoconazole on cotton, rice and wild rice. For domestic uses, humans may be exposed to difenoconazole in food and drinking water, since difenoconazole may be applied directly to growing crops and application may result in difenoconazole reaching surface and ground water sources of drinking water. There are also residential uses of difenoconazole, so there is exposure in residential or non-occupational settings. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. There is a potential for post-application exposure for workers re-entering treated fields.

Risk assessments have been previously conducted for the existing uses of difenoconazole. This risk assessment considers all of the aforementioned exposure pathways based on the proposed uses of difenoconazole, but also considers the existing uses as well.

3.5 Considerations of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, “Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations,” <http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf>.

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup’s food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 HAZARD CHARACTERIZATION AND DOSE-RESPONSE ASSESSMENT

4.1 Toxicology Studies Available for Analysis

The toxicology database for difenoconazole is complete for evaluating and characterizing difenoconazole toxicity and selecting endpoints for purposes of this risk assessment. All toxicity studies required in accordance with new 40 CFR Part 158 data requirements have been submitted. The Hazard and Science Policy Council (HASPOC) concluded that a 28-day inhalation toxicity study is not required at this time (TXR 0054074).

4.2 Absorption, Distribution, Metabolism and Excretion (ADME)

The absorption, distribution, metabolism, and excretion of difenoconazole were studied in rats. In one study, the test compound was labeled with C¹⁴ at either the phenyl or triazole ring. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg of radiolabeled compound or 0.5 mg/kg unlabeled compound by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [¹⁴C]-difenoconazole on day 15. In a second follow-up study [¹⁴C]-difenoconazole (phenyl ring label) was administered as single oral gavage dose of 0.5 or 300 mg/kg. The second study was conducted to address deficiencies in the initial study by providing biliary excretion and identification of metabolites.

Difenoconazole was rapidly absorbed and extensively distributed, metabolized, and excreted in rats for all dosing regimens. Distribution, metabolism and elimination of difenoconazole were not sex related in the first study. Recovery of administered dose was 96-108%. Biliary excretion, examined in the second study, constituted the main route of elimination with some dose and sex dependency (75% at the low dose for both sexes; 56% for males and 39% for females at the high dose). Urinary and fecal eliminations exhibited a dose-related pattern at 48 hours. In bile duct cannulated rats, 9-14% of dose was eliminated in the urine at the low dose versus 1% in the high-dose rats. In bile duct cannulated rats, 2-4% was eliminated in the feces at the low dose versus 17-22% at the high dose. Half-lives of elimination are approximately 20 hours for the low dose groups and 33-48 hours for the high dose group. Radioactivity in the blood peaked at 2 to 4 hours at the low and high dose respectively.

Difenoconazole undergoes successive oxidation and conjugation reactions. Following administration of 300 mg/kg of (¹⁴C-phenyl) difenoconazole, three major urinary metabolites were identified as CGA 205375 and HO-CGA 205375 (6% of dose), sulfate conjugates (and their isomers) of HO-205375 (3.9% of dose), and the hydroxyacetic metabolite of HO-CGA 205375 (2.0% of dose). No single unknown urinary metabolite accounted for >1.1% of the dose. Free triazole metabolite was detected in the urine of the triazole-label groups and its byproduct was detected in the liver of phenyl labeled groups only.

The study results indicate that difenoconazole and/or its metabolites do not bioaccumulate appreciably following oral exposure since all tissues contained negligible levels (<1%) or radioactivity 7-days post exposure.

A dermal absorption factor of 6% was derived based on data from a triple pack of a rat *in vivo* dermal absorption study and *in vitro* dermal absorption studies conducted with rat and human skin (TXR 0056473). Inhalation toxicity is assumed to be equivalent to oral toxicity.

4.3 Toxicological Effects

Subchronic and chronic studies with difenoconazole in mice and rats showed decreased body weights, decreased body weight gains and effects on the liver (e.g. hepatocellular hypertrophy, liver necrosis, fatty changes in the liver). No systemic toxicity was observed at the limit dose in the most recently submitted 28-day rat dermal toxicity study.

The available toxicity studies indicated no increased susceptibility of rats from *in utero* or postnatal exposure to difenoconazole. In prenatal developmental toxicity studies in rats and in the two-generation reproduction study in rats, fetal/offspring toxicity, when observed, occurred at equivalent or higher doses than in the maternal/parental animals. However, in rabbits there was qualitative susceptibility since the developmental effects were more severe than the maternal effects seen at the same dose. However, the POD selected to assess acute dietary exposures is protective from these effects.

In a rat developmental toxicity study, developmental effects were observed at doses higher than those which caused maternal toxicity. Developmental effects in the rat included increased incidence of ossification of the thoracic vertebrae and hyoid, decreased number of sternal centers of ossification, increased number of ribs and thoracic vertebrae, and decreased number of lumbar vertebrae. In the rabbit study, developmental effects (increases in post-implantation loss and resorptions and decreases in fetal body weight) were also seen at maternally toxic (decreased body weight gain and food consumption) doses. In the two-generation reproduction study in rats, toxicity to the fetuses/offspring, when observed, occurred at equivalent or higher doses than in the maternal/parental animals.

In an acute neurotoxicity study in rats, reduced fore-limb grip strength was observed on day 1 in males at the LOAEL of 200 mg/kg. The effect in males is considered transient since it was not observed at later observation points. Toxicity in females was observed only at the limit dose (2000 mg/kg). In a subchronic neurotoxicity study in rats, decreased hind limb strength was observed in males only at doses ≥ 17.5 mg/kg/day. The effects observed in acute and subchronic neurotoxicity studies are transient and found in one sex (males) with no histologic findings and the selected endpoints of toxicity for risk assessment are protective of any potential neurotoxicity. Based on the toxicity profile, and lack of concern for neurotoxicity, a developmental neurotoxicity study in rats is not required.

In an immunotoxicity study in mice difenoconazole produced immunotoxicity at doses that caused systemic toxicity.

In accordance with HED's current policy and EPA's 2005 Cancer Guidelines, difenoconazole is classified as "Suggestive Evidence of Carcinogenic Potential" based on liver tumors observed in mice at 300 ppm (46.3 mg/kg/day) and higher, the absence of tumors at two lower doses of 10 and 30 ppm (1.5 and 4.6 mg/kg/day, respectively), excessive toxicity observed at the two highest

doses of 2500 and 4500 ppm (423 and 819 mg/kg/day, respectively), the absence of genotoxicity and no evidence of carcinogenicity in rats (TXR 0054532). HED's Cancer Peer Review Committee recommended use of an MOE approach to risk assessment using the chronic point of departure (POD) based on effects observed in the chronic mouse study relevant to tumor development (*i.e.*, hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis). The chronic POD is considered protective of the cancer effects.

Difenoconazole possesses low acute toxicity by the oral, dermal and inhalation routes of exposure. It is not an eye or skin irritant and is not a sensitizer.

The complete toxicity profile for difenoconazole is provided in Appendix A.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

Based on the lack of quantitative or qualitative sensitivity and complete toxicity database for difenoconazole, the FQPA factor for increased susceptibility to infants and children may be reduced to 1x.

4.4.1 Completeness of the Toxicology Database

The toxicity database is sufficient for a full hazard evaluation and is considered adequate to evaluate risks to infants and children. The Hazard and Science Policy Council (HASPOC) concluded that a 28-day inhalation toxicity study is not required at this time (TXR 0054074).

4.4.2 Evidence of Neurotoxicity

There are no clear signs of neurotoxicity following acute, subchronic or chronic dosing in multiple species in the difenoconazole database. The effects observed in acute and subchronic neurotoxicity studies are transient, and showed in one sex (males as reduced fore-limb grip strength with no histologic findings) and the selected endpoints of toxicity for risk assessment are protective of any potential neurotoxicity.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

The available Agency guideline studies indicated no increased qualitative or quantitative susceptibility of rats to *in utero* and/or postnatal exposure to difenoconazole. However, in rabbits there was qualitative susceptibility since the developmental effects were more severe than the maternal effects seen at the same dose. However, the POD selected to assess acute dietary exposures is protective from these effects.

In a rat developmental toxicity study developmental effects were observed at doses higher than those which caused maternal toxicity. In the rabbit study, developmental effects (increases in post-implantation loss and resorptions and decreases in fetal body weight) were also seen at maternally toxic doses (decreased body weight gain and food consumption). Because these effects are more severe, qualitative susceptibility is evident in the rabbit. In the two-generation

reproduction study in rats, toxicity to the fetuses/offspring, when observed, occurred at equivalent or higher doses than in the maternal/parental animals.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. The dietary risk assessment is conservative (tolerance level residues and 100% crop treated for the acute while the chronic used USDA Pesticide Data Program (PDP) monitoring data, average field trial residues for some commodities, tolerance level residues for remaining commodities, and average percent crop treated for some commodities) and will not underestimate dietary exposure to difenoconazole.

4.5 Toxicity Endpoint and Point of Departure Selections

4.5.1 Dose-Response Assessment

Toxicity endpoints and points of departure (PODs) for dietary (food and water), occupational, and residential exposure scenarios are summarized below. A detailed description of the studies used as a basis for the selected endpoints are presented in Appendix A.

An acute POD of 25 mg/kg/day (NOAEL) was selected from an acute neurotoxicity study in rats based on reduced fore-limb grip strength in males on day 1 at the LOAEL of 200 mg/kg/day. An uncertainty factor (UF) of 100x (10x to account for interspecies extrapolation and 10x for intraspecies variation) was applied to the NOAEL to obtain an acute reference dose (aRfD) of 0.25 mg/kg/day. Since the FQPA factor has been reduced to 1X, the acute population adjusted dose (aPAD) is equivalent to the aRfD. The selected endpoint is considered appropriate for acute dietary exposure because effects were seen after a single dose. The endpoint is protective of the general population and all subpopulations for effects seen in the acute neurotoxicity study in rats. It is also protective of developmental and maternal effects observed in the rabbit developmental toxicity study at the LOAEL of 75 mg/kg/day (NOAEL of 25 mg/kg/day).

A chronic POD of 0.96 mg/kg/day (NOAEL) was selected from a chronic toxicity/carcinogenicity oral study in rats based on cumulative decreases in body weight gains in males observed at the LOAEL of 24 mg/kg/day. A UF of 100x (10x to account for interspecies extrapolation and 10x for intraspecies variation) was applied to the dose to obtain a chronic reference dose (cRfD/cPAD) of 0.01 mg/kg/day. Since the FQPA factor has been reduced to 1X, the chronic population adjusted dose (cPAD) is equivalent to the cRfD.

Short-term incidental oral and short- and intermediate-term dermal and inhalation PODs of 1.25 mg/kg/day were selected from a two generation reproduction study in rats based on decreased pup weight in males at 12.5 mg/kg/day (LOAEL) on day 21, and reductions in body weight gain in F0 females. Although dermal toxicity studies are available, a POD from an oral study was selected because effects in young animals (decreased pup weight) the primary effect of concern for short-, intermediate- and long-term exposure is not specifically evaluated in the available dermal toxicity studies that only assess adult animals. The selected endpoint is protective of offspring effects from dermal exposure. An MOE of 100 is the level of concern (LOC) for the short- and intermediate-term dermal and inhalation exposure scenarios based on the conventional

uncertainty factor of 100 (10x for interspecies extrapolation and 10x for intraspecies variation).

A dermal absorption factor (DAF) is applied when dermal exposure endpoints are selected from oral toxicity studies. The dermal factor converts the oral dose to an equivalent dermal dose for the risk assessment. A DAF of 6% was selected for use in risk assessment based on available *in vivo* dermal absorption studies in rat and *in vitro* dermal absorption studies conducted with rat and human skin (TXR 0056473).

4.5.2 Recommendations for Combining Exposure Routes for Risk Assessment

When there are potential residential exposures to the pesticide, the aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. The common toxicological effect for the oral, dermal, and inhalation routes is related to body weight and; therefore, these routes of exposure should be combined.

4.5.3 Cancer Classification and Risk Assessment Recommendations

Difenoconazole is not mutagenic, and no evidence of carcinogenicity was seen in rats. Evidence for carcinogenicity was seen in mice, where liver tumors were induced at doses which were considered to be excessively high for carcinogenicity testing. Liver tumors were observed in mice at 300 ppm and higher; however, based on excessive toxicity observed at the two highest doses of 2500 and 4500 ppm (females terminated after two weeks due to excessive toxicity resulting in moribundity and death), the absence of tumors at two lower doses of 10 and 30 ppm, the absence of genotoxic effects, and no evidence of carcinogenicity in rats. In accordance with HED's current policy and EPA's 2005 Cancer Guidelines, difenoconazole is classified as "Suggestive Evidence of Carcinogenic Potential," based on excessive toxicity observed at the two highest doses, the absence of tumors at the lower doses and the absence of genotoxic effects (TXR 0054532). Based on the CPRC recommendation, the risk assessment uses an (MOE) approach utilizing the no-observable-adverse-effects-level (NOAEL) of 30 ppm (4.7 and 5.6 mg/kg/day in males and females, respectively) and the lowest-observable-adverse-effects-level (LOAEL) of 300 ppm (46 and 58 mg/kg/day in males and females, respectively) from the mouse study using only those biological endpoints which were relevant to tumor development (*i.e.*, hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis). The Agency has concluded that a non-linear RfD approach is appropriate for assessing cancer risk to difenoconazole and a separate quantitative cancer exposure assessment is unnecessary since the chronic dietary risk uses the chronic POD from the rat carcinogenicity study of 0.96 mg/kg/day based on bodyweight effects which will be protective of potential cancer risk.

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Risk Assessment

Toxicological doses/endpoints selected for the difenoconazole risk assessment are provided in Tables 4.5.4.1 and 4.5.4.2.

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Difenoconazole for Use in Dietary and Non-Occupational Human Health Risk Assessments

Exposure Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, LOC for Risk Assessment	Study and Relevant Toxicological Effects
Acute Dietary (All populations)	NOAEL = 25 mg/kg/day	UF _A = 10X UF _H = 10X FQPA SF = 1X	aRfD = aPAD = 0.25 mg/kg/day	Acute Neurotoxicity Study in Rats (MRID 46950327) LOAEL= 200 mg/kg in males based on reduced fore-limb grip strength in males on Day 1 and increased motor activity on Day 1.
Chronic Dietary (All populations)	NOAEL = 0.96 mg/kg/day	UF _A = 10X UF _H = 10X FQPA SF = 1X	cRfD = cPAD = 0.01mg/kg/day	Combined chronic toxicity/carcinogenicity (rat; dietary, MRID 42090019, 42710010) LOAEL = 24.1/32.8 mg/kg/day (M/F) based on cumulative decreases in body-weight gains (-6 to -11% of the controls).
Incidental Oral Short-Term (1-30 days)	Oral NOAEL = 1.25 mg/kg/day	UF _A = 10X UF _H = 10X FQPA SF = 1X	Residential LOC for MOE<100	Reproduction and fertility Study (rat; dietary, MRID 42090018) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 (-7%) and reduction in body-weight gain of F ₀ females prior to mating, gestation and lactation (-17% to -42% compared to controls).
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months)	Oral NOAEL = 1.25 mg/kg/day DAF = 6%	UF _A = 10X UF _H = 10X FQPA SF = 1X	Residential LOC for MOE<100	Reproduction and fertility Study (rat; dietary, MRID 42090018) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F ₀ females prior to mating, gestation and lactation.
Inhalation (Short- and Intermediate-term) *Inhalation and oral absorption assumed equivalent	Oral NOAEL = 1.25 mg/kg/day	UF _A = 10X UF _H = 10X FQPA SF = 1X	Residential LOC for MOE<100	Reproduction and fertility Study (rat; dietary, MRID 42090018) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F ₀ females prior to mating, gestation and lactation.
Cancer (oral, dermal, inhalation)	Difenoconazole is classified "Suggestive Evidence of Carcinogenic Potential" with a non-linear (MOE) approach for human risk characterization (CPRC Document, 7/27/94, Memo, P. V. Shah dated March 3, 2007, HED Doc. No. 0054532).			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. DAF = Dermal Absorption Factor.

Table 4.5.4.2. Summary of Toxicological Doses and Endpoints for Difenoconazole for Use in Occupational Human Health Risk Assessments

Exposure Scenario	Point of Departure	Uncertainty/FQ PA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short- and Intermediate-Term (1-30 days and 1-6 months)	Oral NOAEL = 1.25 mg/kg/day DAF = 6%	UF _A = 10X UF _H = 10X	Occupational LOC for MOE<100	Reproduction and fertility Study (rat; dietary, MRID 42090018) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F ₀ females prior to mating, gestation and lactation.
Inhalation (Short- and Intermediate-term) *Inhalation and oral absorption assumed equivalent	Oral NOAEL = 1.25 mg/kg/day	UF _A = 10X UF _H = 10X	Occupational LOC for MOE<100	Reproduction and fertility Study (rat; dietary, MRID 42090018) Parental/Offspring LOAEL = 12.5 mg/kg/day based on decreased pup weight in males on day 21 and reduction in body-weight gain of F ₀ females prior to mating, gestation and lactation.
Cancer (oral, dermal, inhalation)	Difenoconazole is classified “Suggestive Evidence of Carcinogenic Potential” with a non-linear (MOE) approach for human risk characterization (CPRC Document, 7/27/94, Memo, P. V. Shah dated March 3, 2007, HED Doc. No. 0054532).			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. DAF = Dermal Absorption Factor. N/A = not applicable.

5.0 DIETARY EXPOSURE AND RISK ASSESSMENT

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

The nature of the residue in plants is understood based on acceptable plant metabolism studies reflecting foliar applications in canola, grape, potato, tomato, and wheat, and seed treatment in wheat. The residue of concern for both tolerance enforcement and risk assessment for crops included in this petition is difenoconazole only. The nature of the residue in livestock is understood based on acceptable goat and hen metabolism studies. The residues of concern for both tolerance enforcement and risk assessment for livestock commodities are difenoconazole and its metabolite CGA-205375. In addition, metabolite OH-CGA-169374, which comprised 15% of the TRR in goat milk from the phenyl-labeled study, should be considered as a residue of concern in milk for the dietary risk assessment.

The nature of the residue in rotational crops is adequately understood. The metabolism of difenoconazole in rotational crops is similar to that of primary crops. The available difenoconazole confined and limited field rotational crop trials are deemed adequate to satisfy data requirements under Guidelines 860.1850 and 860.1900. Taken together, these data support

a 30-day plantback interval (PBI) for cereal and root/tuber crops not already registered for foliar use with difenoconazole and a 60-day PBI for all other crops not already registered for foliar use with difenoconazole. With these PBIs, tolerances for residues of difenoconazole are not needed for rotational crops.

5.1.2 Summary of Environmental Degradation

Difenoconazole has potential to reach surface water via run-off, erosion, and spray drift, and is less likely to reach ground water except in soils of high sand and low organic matter content. Environmental fate data indicate that difenoconazole is relatively stable to aerobic and anaerobic soil metabolisms and aerobic and anaerobic aquatic metabolism. When applied at 0.1-0.23 ppm to an aerobic soil, difenoconazole appears to degrade with half-lives ranging from 84.5 to 533 days based on laboratory studies conducted on a variety of foreign and domestic soils. At concentrations of 10 ppm, difenoconazole degraded with the half-lives of 1059-1600 days in aerobic, and 947 days anaerobic loam soil, respectively. In aquatic environment under aerobic conditions, difenoconazole microbially degraded with half-lives ranging from 315 to 565 days at concentrations up to 0.17 mg ai/L, and 860 days in a concentration of 10 mg ai/L. Under anaerobic conditions, difenoconazole degraded in 370 days at a concentration of 0.04 mg ai/L, and 1245 days at concentrations of 10 mg ai/L. The longer half-life values obtained for those higher concentration rates may imply that the rate of difenoconazole microbially mediated degradation may be concentration dependent. In laboratory studies on difenoconazole a significant amount of radioactivity was nonextractable (14.4 to 48.9%) from soils.

Considering abiotic degradation, difenoconazole is photolyzed in water (half-life of 6 to 228 days), but stable in soil. The half-life of 228 days was extrapolated from a 15-day study in which difenoconazole slowly photolyzed from 100% to 91% under artificial light conditions (MRID 46950105). Also, the compound is stable to hydrolysis at pH values from 4 to 9.

Difenoconazole degraded with half-lives ranging from 139 to 462 days in the terrestrial field dissipation studies. The overall stability of the compound in the terrestrial environment suggests that difenoconazole may accumulate in soil with successive applications from year to year.

5.1.3 Comparison of Metabolic Pathways

Little information is available on the toxicity of the major difenoconazole metabolites. The CGA-205375 metabolite formed in livestock appears to be formed in the rat also and is, therefore, part of the total toxic exposure for these animals.

5.1.4 Residues of Concern Summary and Rationale

Residues of concern were determined based on recommendations from the HED Residues of Concern Knowledgebase Sub-committee (ROCKS) (D391350, 9/19/11). The residue of concern for plant commodities for tolerance enforcement and risk assessment purposes is difenoconazole only. The HED ROCKS has determined that the parent compound and the CGA-205375 metabolite are the residues of concern in livestock commodities for both the tolerance

enforcement and the risk assessment. In addition, metabolite OH-CGA-169374, which comprised 15% of the TRR in goat milk from the phenyl-labeled study, should be considered as a residue of concern in milk for the dietary risk assessment. Based on available goat metabolism data, total residues of concern in milk for dietary risk assessments (parent, CGA-205375 and OH-CGA-169374), should be calculated by multiplying the tolerance in milk by a factor of 1.5x. Table 5.1.4.1 summarizes tolerance expression and the residues of concern in plant and livestock commodities.

Difenoconazole belongs to the triazole group of fungicides. The triazole metabolites common to the group, 1,2,4-triazole (1,2,4-T), triazolylalanine (TA) and triazolylacetic acid (TAA), are residues of concern for risk assessment purposes and are assessed separately from the parent compound.

Table 5.1.4.1. Difenoconazole Residues of Concern in Plants and Ruminants.			
Matrix		Residues of Concern	
		For Risk Assessment	For Tolerance Expression
Plants	Primary and Rotational crops	Parent Only	Parent Only
Livestock	Ruminant and Poultry	Parent and CGA 205375	Parent and CGA 205375
	Milk	Parent, CGA 205375 and OH-CGA-169374	Parent and CGA 205375
Drinking Water		Parent and CGA 205375	NA

Note: The triazole-containing metabolites 1,2,4-T, TA, and TAA should be included in the residues of concern for risk assessment purposes only for plant and livestock commodities. Since these metabolites are common to the entire class of triazole-containing fungicides and because of differential toxicity between metabolites and the various parent compounds, risks associated with exposure to 1,2,4-T and to TA/TAA are addressed separately.

5.2 Food Residue Profile

5.2.1 Residues in Crops

Syngenta submitted twelve cotton field trials for difenoconazole conducted in the United States during the 2014 growing season and seventeen rice field trials for difenoconazole conducted in the United States during the 2013 and 2014 growing seasons. Cotton trials were conducted in the North American Free Trade Agreement (NAFTA) Growing Zones 2 (GA; 1 trial), 4 (LA, MO, and MS; 3 trials), 6 (TX; 1 trial), 8 (OK and TX; 4 trials), and 10 (CA; 3 trials). Rice trials were conducted in the NAFTA Growing Zones 4 (AR, LA, MO, and MS; 11 trials), 5 (MO; 1 trial), 6 (TX; 3 trials) and 10 (CA; 2 trials). Each field trial site consisted of one untreated plot and two side-by-side treated plots. At each trial location, treated plots received applications of an emulsifiable concentrate (EC) formulation or a suspension concentrate (SC) formulation of difenoconazole at the maximum proposed use rates. A nonionic surfactant (NIS) or crop oil concentrate (COC) was added to all spray mixtures. Samples were harvested at the proposed PHIs and analyzed for all difenoconazole and the triazole metabolites.

The submitted cotton, undelinted seed and cotton gin byproducts field trial data, conducted side-by-side with either an EC or SC formulation of difenoconazole, are adequate to support the proposed use pattern for cotton. The submitted field trial data were collected with adequate data-

collection methods and are supported by adequate storage stability data. There was no significant difference between residues of difenoconazole in/on cottonseed, undelinted, seed resulting from the EC formulation vs. the SC formulation based on a statistical analysis of the data. There were too few cotton gin byproducts data for a meaningful statistical test; however, residues were substantially similar.

The submitted rice grain field trial data, conducted side-by-side with either an EC or SC formulation of difenoconazole, are adequate to support the proposed use pattern for rice and wild rice. The submitted field trial data were collected with adequate data-collection methods and are supported by adequate storage stability data. There was no significant difference between residues of difenoconazole in/on rice grain resulting from the EC formulation vs. the SC formulation based on a statistical analysis of the data. Although rice straw field trial data were submitted, rice straw is no longer considered a significant feedstuff and a tolerance is not required for this commodity.

Syngenta submitted cottonseed and rice processing data which are adequate to support the proposed uses of difenoconazole on cotton and rice. Residues of difenoconazole did not concentrate in/on the processed cottonseed commodities of meal, hulls, and refined oil (median processing factors $\leq 0.2x$) or the processed rice commodities of polished rice or bran ($< 0.1x$ and $0.7x$). Residues of difenoconazole did concentrate in rice hulls (processing factor of $3.3x$); however, rice hulls are no longer considered a significant feedstuff and a tolerance in/on this commodity is not required.

The side-by-side trials for the two formulations were not deemed independent and residues for each test site were averaged for the tolerance determination. Using the Organization for Economic Cooperation and Development (OECD) tolerance calculation procedures, the recommended tolerances for residues of difenoconazole are 0.40 ppm in/on cottonseed subgroup 20C, 15 ppm in/on cotton gin byproducts, 7.0 ppm in/on rice, grain and 7.0 ppm in/on rice, wild, grain. Based on the submitted cotton and rice processing data, separate tolerances are not needed for processed commodities of cotton and rice. The recommended tolerance in/on cottonseed subgroup 20C for foliar use of difenoconazole is deemed adequate to cover residues which might be incurred from both the proposed foliar use and the currently registered cottonseed treatment use; hence the currently established tolerance in/on cotton, undelinted seed (0.05 ppm) is no longer needed and should be removed. The recommended tolerances are the same as the petitioned-for tolerances.

5.3 Water Residue Profile

5.3.1 Estimated Drinking Water Concentrations

The estimated drinking water concentrations (EDWCs) used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED; Memo, F. Khan, 5-October-2016; D432384). EDWCs were generated using the maximum annual rate of 0.34 lb ai/A/year (0.114 lb ai/A x 3 applications) for cotton/cottonseed with the Tier II Pesticide in Water Calculator (PWC v1.52; December 8, 2015) model. The Revised Tier I Rice model (v1.0, May 8, 2007) was also used to generate EDWCs for the maximum annual rate of 0.244 lb ai/A/year (0.122 lb ai/A x 2 applications) for rice/wild rice. Since the groundwater module was incorporated into the PWC model, EDWCs for groundwater were revised using the maximum annual rate of 0.50 lb ai/A/year (0.125 lb ai/A x 4 applications) for citrus, which is the highest application rate/A/year among all difenoconazole uses (USEPA, 2015, D428500). The rationale for using the highest application rate of difenoconazole is to simulate the maximum EDWCs for groundwater to support residue of concern of difenoconazole and its degradates for drinking water sources from groundwater.

For surface water, the EDWCs for rice/wild rice uses exceeded the previously recommended peak (acute) concentration of 20.0 µg/L and annual mean (non-cancer chronic) concentration of 13.6 µg/L (US EPA, 2014, D421092). The maximum EDWCs of 33.4 µg/L for the annual peak exposure and 27.8 µg/L for the annual mean exposure were observed in surface water based on difenoconazole use on rice/wild rice. However, the EDWCs in paddy water do not account for dilution and degradation as rice paddy water is released into and mixed with flowing surface water and therefore the EDWCs are likely to be lower due to degradation and dilution of difenoconazole and its degradate. Since Tier 1 Rice model is based on one-year simulation, the recommended 30-year annual average concentration (cancer chronic) of 9.9 µg/L reported in the latest drinking water assessments (US EPA, 2014, D421092) remains unchanged.

For groundwater, the highest difenoconazole EDWCs in groundwater are 2.0 µg/L for peak and 0.6 µg/L for the simulation average. However, there was no breakthrough observed using 100-year simulation. High adsorption coefficient of 5381 mL/g of difenoconazole may have slowed the leaching of difenoconazole into the subsurface of application scenarios.

Recommended EDWCs for human health are **33.4 µg/L (ppb)** for the acute dietary (food plus water) exposure analysis and the 1-in-10 year annual mean EDWC of **27.8 µg/L (ppb)** for the chronic dietary (food plus water) exposure analysis.

Table 5.3.1.1. Recommended EDWCS for Total Toxic Residues of Difenoconazole Use on Cotton, Cotton Seed, Rice and Wild Rice.

Source	Peak Exposure (µg/L)	Annual Mean Exposure (µg/L)	30-year Average Exposure (µg/L)
Surface water	33.4 ^A	27.8 ^A	9.9 ^B
Groundwater ^C	2.0	0.60	--

^A EDWCs generated using Tier 1 Rice model for aerial application of 0.244 lb ai/A/Y for rice/wild rice use and the release of irrigation or flooded paddy water for 7 days after the last application

^B EDWCs generated using the Surface Water Concentration Calculator (SWCC) model for aerial application of 0.46 lb ai/A/Y for grape use as recommended in previous drinking water assessments (USEPA, 2014).

^C Groundwater EDWCs are based on the PWC (PRZM-GW module) 100 years simulation for FL citrus scenario and the highest difenoconazole application rate of 0.50 lb ai/A/Y for citrus

Drinking Water Assessment for Triazoles Metabolites

Residues of 1,2,4-triazole in drinking water were provided to HED by EFED (I. Maher, DP320682, 28 Feb 2006). Due to the inter-conversion between 1,2,4-triazole, triazole alanine, and triazole acetic acid that may occur in the environment, the residue estimates used in these assessments are a summation of all three residues and, therefore, represent an overestimate of actual concentrations of the common triazole metabolites in drinking water. The Tier II PRZM/EXAMS (surface water) and SCIGROW (ground water) residue estimates are summarized in Table 5.3.1.2. HED notes that there were no detects of 1,2,4-triazole in any of the 271 water samples analyzed by PDP, with a limit of quantification of 730 parts per trillion (0.73 ppb). The surface water estimates are significantly greater than those for ground water, and were used in the assessments for free triazole as well as the conjugated metabolites.

Table 5.3.1.2. Summary of Estimated Drinking Water Concentrations of 1,2,4-Triazole.

Exposure Duration	Surface Water Concentration, ppm	Ground Water Concentration, ppm
Acute	0.041	0.001
Chronic	0.011	0.001

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

Unrefined acute and refined chronic dietary and drinking water exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database DEEM-FCID, Version 3.16, which incorporates consumption data from USDA's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA). This dietary survey was conducted from 2003 to 2008. Dietary risk assessment incorporates both exposure and toxicity of a given pesticide. For acute and chronic dietary assessments, the risk is expressed as a percentage of a maximum acceptable dose (*i.e.*, the dose which HED has concluded will result in no unreasonable adverse health effects). This dose is referred to as the population adjusted dose (PAD). The PAD is equivalent to the reference dose (RfD) divided by the additional Safety Factor, if applied. For acute and non-cancer chronic exposures, HED is concerned when estimated dietary risk exceeds 100% of the PAD.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The acute dietary exposure analyses assumed 100% crop treated (CT). Average %CT was used in the chronic dietary exposure analysis for the following crops: almond 10%, apple 20%, apricot 10%, broccoli 2.5%, Brussels sprouts 2.5%, cabbage 5%, cantaloupe 2.5%, carrot 5%, cauliflower 2.5%, cherry 2.5%, cucumber 5%, garlic 5%, grape 10%, grapefruit 2.5%, hazelnut 1%, nectarine 2.5%, onions 5%, orange 2.5%, peach 2.5%, pear 10%, pecan 2.5%, pepper 5%, pistachio 5%, plum/prune 10%, potato 20%, pumpkin 2.5%, soybean 2.5%, squash 5%, strawberry, 2.5%, sugar beet 15%, tangerine 2.5%, tomato 25%, walnut 1%, watermelon 5%, and wheat (seed treatment) 10%. These average %CT estimates (Screening Level Usage Analysis (SLUA) dated 5/9/16) were updated since the most recent dietary risk assessment conducted for difenoconazole (D426491, T. Morton, 7/1/15).

5.4.3 Acute Dietary Risk Assessment

A new unrefined acute dietary assessment was conducted for the proposed new uses. The unrefined acute analysis assumed tolerance-level residues, 100% crop treated (CT), available empirical or DEEM (ver. 7.81) default processing factors and a Tier 1 drinking water estimate. The resulting acute food plus water dietary exposure estimates were less than HED's level of concern (<100% of the aPAD) at the 95th percentile of the exposure distribution for the general U.S. population (17% aPAD) and all population sub-groups. The most highly exposed population subgroup was All Infants with 53% aPAD. See Table 5.4.3.1.

Table 5.4.3.1. Summary of Acute Dietary (Food plus Water) Exposure and Risk for Difenoconazole at the 95th Percentile.			
Population Subgroup	aPAD (mg/kg/day)	Exposure (mg/kg/day)	%aPAD
General U.S. Population	0.25	0.042473	17
All Infants (< 1 year old)		0.131450	53
Children 1-2 years old		0.114077	46
Children 3-5 years old		0.081837	33
Children 6-12 years old		0.053208	21
Youth 13-19 years old		0.027894	11
Adults 20-49 years old		0.030394	12
Adults 50-99 years old		0.030544	12
Females 13-49 years old		0.029734	12

The bolded %aPAD is the highest.

5.4.4 Chronic Dietary Risk Assessment

A new refined chronic non-cancer dietary assessment was conducted for the proposed uses of difenoconazole. The refined chronic analysis assumed tolerance-level residues for some commodities, average field trial residues and USDA Pesticide Data Program monitoring samples for the remaining commodities, available empirical or DEEM (ver. 7.81) default processing factors, average % CT assumptions for some commodities and a Tier 1 drinking water estimate.

The resulting chronic non-cancer food plus water dietary exposure estimates were less than HED's level of concern (<100% of the cPAD) for the general U.S. population (18% cPAD) and all population sub-groups. The most highly exposed population subgroup was All Infants with 50% cPAD. See Table 5.4.4.1. A separate cancer dietary assessment was not conducted for difenoconazole because the cancer NOAEL is higher than the chronic RfD; therefore, the chronic dietary risk estimate is considered protective of all chronic effects including carcinogenicity.

Table 5.4.4.1. Summary of Chronic Dietary (Food plus Water) Exposure and Risk for Difenoconazole.			
Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)	%cPAD
General U.S. Population	0.01	0.001812	18
All Infants (< 1 year old)		0.005043	50
Children 1-2 years old		0.004566	46
Children 3-5 years old		0.003232	32
Children 6-12 years old		0.002091	21
Youth 13-19 years old		0.001341	13
Adults 20-49 years old		0.001622	16
Adults 50-99 years old		0.001539	15
Females 13-49 years old		0.001491	15

The bolded %cPAD is the highest.

5.4.5 Summary Findings of Separate Dietary Assessment for Triazole Metabolites

The dietary exposure analyses for the triazole metabolites was updated for the proposed new uses of difenoconazole on cotton, rice and wild rice (D435630, T. Morton, 11/2/2016). Addition of the new uses of difenoconazole did not significantly change the previous dietary exposure assessment for the triazole metabolites. The results from the triazole dietary analysis are below HED's level of concern; see Table 5.4.5.1.

Table 5.4.5.1. Summary of Dietary (Food and Drinking Water) Exposure and Risk for the Common Triazole Metabolites Adding the New Uses for Difenoconazole.						
Population Subgroup	Acute Dietary (95 th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
1,2,4-Triazole						
General U.S. Population	0.008265	28	0.001177	24	Not Applicable	Not Applicable
All Infants (< 1 year old)	0.012366	41	0.001977	40		
Children 1-2 years old	0.023032	77	0.003601	72		
Children 3-5 years old	0.018902	63	0.002789	56		
Children 6-12 years old	0.010990	37	0.001493	30		
Youth 13-19 years old	0.007176	24	0.000945	19		
Adults 20-49 years old	0.006554	22	0.000987	20		
Adults 50-99 years old	0.005752	19	0.000934	19		
Females 13-49 years old	0.0066744	22	0.000960	19		

Table 5.4.5.1. Summary of Dietary (Food and Drinking Water) Exposure and Risk for the Common Triazole Metabolites Adding the New Uses for Difenoconazole.

Population Subgroup	Acute Dietary (95 th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
Triazolyalanine + Triazolyacetic Acid						
General U.S. Population	Not Applicable	Not Applicable	0.016200	18	Not Applicable	Not Applicable
All Infants (< 1 year old)			0.022890	25		
Children 1-2 years old			0.055093	61		
Children 3-5 years old			0.042904	48		
Children 6-12 years old			0.022266	25		
Youth 13-19 years old			0.013481	15		
Adults 20-49 years old			0.012944	14		
Adults 50-99 years old			0.012157	14		
Females 13-49 years old			0.012559	14		
	0.077748	78				

* The values for the highest exposed population for each type of risk assessment are bolded.

6.0 RESIDENTIAL (NON-OCCUPATIONAL) EXPOSURE/RISK CHARACTERIZATION

There are no proposed new residential uses associated with this new petition; however, there are existing residential uses that have been previously reassessed to reflect updates to HED's 2012 Residential SOPs¹ along with policy changes for body weight assumptions. The revised residential exposure estimates impact the human health aggregate risk assessment for difenoconazole.

Based on the existing exposure pattern, residential exposure scenarios have been identified from treatment of ornamental plants in commercial and residential landscapes and interior plantscapes. Potential exposure is expected to homeowners handling the product and/or from performing post-application activities in treated areas. There are no residential uses for difenoconazole that would result in incidental oral exposure to children.

Representative outdoor and indoor residential handler and post-application exposure scenarios were previously reassessed for all difenoconazole uses in accordance with the Revised Residential SOPs (2012), and the risk estimates were not of concern (D421188, I. Nieves, 2/24/2015). Table 6.0.1 presents a summary of the residential handler non-cancer exposure and risk estimates for the registered scenarios (Total MOEs ranged from 3,500 to 68,000; LOC =100). Table 6.0.2 summarizes the residential post-application non-cancer exposure and risk estimates for all difenoconazole uses (MOEs ranged from 250 to 31,000; LOC=100).

¹ Available: <http://www.epa.gov/pesticides/science/residential-exposure-sop.html>

Table 6.0.1. Residential Handler Non-Cancer Exposure and Risk Estimates for Difenoconazole.

Table 6.0.1. Residential Handler Non-Cancer Exposure and Risk Estimates for Dinotolazole.										
Exposure Scenario	Level of Concern	Dermal Unit Exposure (mg/lb ai)	Inhalation Unit Exposure (mg/lb ai)	Maximum Application Rate ¹	Area Treated or Amount Handled Daily ²	Dermal		Inhalation		Total
						Dose (mg/kg/day) ³	MOE ⁴	Dose (mg/kg/day) ⁵	MOE ⁶	MOE ⁷
Mixer/Loader/Applicator on Ornamentals (Garden/Trees) with Liquid Formulation										
Manually-pressurized handwand	100	63	0.018	3.0x10 ⁻⁶ lb ai/ft ² (0.13 lb ai/A)	1,200 ft ²	0.00017	7,400	0.0000008	1,600,000	7,400
Hose-end Sprayer		58	0.0014			0.00016	8,000	0.000000063	20,000,000	8,000
Backpack		130	0.14			0.00035	3,600	0.0000063	200,000	3,500
Ready-to-use Hose-end Sprayer		6.26	0.034			0.000017	74,000	0.0000015	820,000	68,000

1 Based on registered label (EPA Reg. No. 100-1262)

2 Based on HED's 2012 Residential SOPs (<http://www.epa.gov/pesticides/science/residential-exposure-sop.html>).

3 Dermal Dose = Dermal Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A/day or gallons/day) × Dermal Absorption Factor (%) ÷ Body Weight (kg).

4 Dermal MOE = Dermal NOAEL (mg/kg/day) ÷ Dermal Dose (mg/kg/day).

5 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A/day or gallons/day) ÷ Body Weight (kg).

6 Inhalation MOE = Inhalation NOAEL (mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

7 Total MOE = NOAEL (mg/kg/day) ÷ (Dermal Dose + Inhalation Dose).

Table 6.0.2. Residential Post-Application Non-Cancer Exposure and Risk Estimates for Difenoconazole.

Lifestage	Post-application Exposure Scenario		Application Rate ¹	Dose (mg/kg/day) ²	MOEs ³
	Use Site	Route of Exposure			
Adult	Gardens	Dermal	0.13 lb ai/A	0.005	250
Child 6 < 11 years				0.003	360
Adult	Trees and Retail Plants			0.00046	2,700
Child 6 < 11 years				0.00031	4,000
Adult	Indoor Plants			0.000060	21,000
Child 6 < 11 years				0.000041	31,000
Adult	Golfing		Dermal	0.25 lb ai/A	0.00044
Child 11 <16 years		0.00051			2,400
Child 6 < 11 years		0.00060			2,100

1. Based on registered or proposed label (Reg. No. 100-1262).

2. Dose (mg/kg/day) equations provided in D421188, I. Nieves, 2/24/2015: Appendix A.

3. MOE = POD (mg/kg/day) ÷ Dose (mg/kg/day).

Table 6.0.3 reflects the residential risk estimates that are recommended for use in the aggregate assessment for difenoconazole.

- The recommended residential exposure for use in the adult aggregate assessment reflects dermal and inhalation exposure from mixing/loading/applying difenoconazole with a backpack sprayer.
- The recommended residential exposure for use in the adult aggregate assessment reflects dermal exposure from post-application exposure to garden applications.
- The recommended residential exposure for use in the children 6 to 11 years old aggregate assessment reflects dermal exposure from post-application exposure to garden applications.

Table 6.0.3. Recommendations for the Residential Exposures for the Difenoconazole Aggregate Assessment.¹								
Lifestage (Scenario)	Dose (mg/kg/day)^{2,4}				MOE^{3,5}			
	Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total
Residential Handler								
Adult (Backpack Sprayer)	0.00035	0.0000063	N/A	0.00036	3,600	200,000	N/A	3,500
Residential Post-application								
Adult (Garden)	0.005	N/A	N/A	0.0054	250	N/A	N/A	250
Child 6<11 years (Gardens)	0.003	N/A	N/A	0.0030	360	N/A	N/A	360

1 Bolded risk estimates should contribute to the residential exposure portion of the aggregate assessment.

2 Residential Handler Dose = the highest handler dose for each applicable lifestage of all residential handler scenarios assessed. Total = dermal + inhalation.

3 Residential Handler MOE = the MOEs associated with the highest residential handler doses. Total = $1 \div (1/\text{Dermal MOE}) + (1/\text{Inhalation MOE})$.

4 Residential Post-application Dose = the highest post-application dose for each applicable lifestage of all post-application scenarios assessed. Total = dermal + inhalation + incidental oral.

5 Residential Post-application MOE = the MOEs associated with the highest post-application doses. Total = Dermal MOE + Inhalation MOE + Incidental Oral MOE.

6.1 Non-Occupational Residential Bystander Postapplication Inhalation Exposure and Risk Estimates

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (<http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037>). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (<http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219>). During Registration Review, the Agency will utilize this analysis to determine if data (*i.e.*, flux studies, route-specific inhalation toxicological studies) or further analysis is required for difenoconazole.

6.2 Non-Occupational Spray Drift Exposure and Risk Estimates

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom and airblast) employed for difenoconazole. The Agency has been working with the Spray Drift Task Force (a task force composed of various registrants which was developed as a result of a Data Call-In issued by EPA), EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the Agency's Spray Drift website for more information).² The Agency has also developed a policy on how to appropriately consider spray drift as a potential source of exposure in risk assessments for pesticides. The potential for spray drift will be quantitatively evaluated for each pesticide during the Registration Review process which ensures that all uses for that pesticide will be considered concurrently. The approach is outlined in the revised (2012) Standard Operating Procedures for Residential Risk Assessment (SOPs) - Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift. This document outlines the quantification of indirect non-occupational exposure to drift.

7.0 AGGREGATE EXPOSURE/RISK CHARACTERIZATION

In accordance with the FQPA, HED must consider and aggregate pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure.

7.1 Acute & Chronic Aggregate Risk

Acute and chronic aggregate exposures include food plus drinking water exposures. As demonstrated under Section 5.4, acute and chronic aggregate risks are not of concern.

7.2 Short-Term Aggregate Risk

Short term aggregate exposure takes into account residential exposure plus average exposure levels to food and water (considered to be a background exposure level). The short term aggregate risk includes the estimated risk associated with combined risks from average food and drinking water exposures and dermal exposures from post-application exposure to adults and children 6 to 11 years old re-entering a treated garden. Short term aggregate risk estimates are provided in Table 7.2.1.

2 Available: <http://www2.epa.gov/reducing-pesticide-drift>

Table 7.2.1. Short-Term Aggregate Risk Calculations							
Population	Short-Term Scenario						
	NOAEL mg/kg/day	LOC¹	Max Allowable Exposure² mg/kg/day	Average Food and Water Exposure mg/kg/day	Residential Exposure mg/kg/day³	Total Exposure mg/kg/day⁴	Aggregate MOE (food, water, and residential)⁵
Adult Male	1.25	100	0.0125	0.0015	0.0054	0.0069	180
Adult Female				0.0015	0.0054	0.0069	180
Child 6<11 years				0.0021	0.0030	0.0051	250

¹ 10X for interspecies extrapolation, 10X for intraspecies variation.

² Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC.

³ Residential Exposure = [Oral exposure + Dermal exposure + Inhalation Exposure]. Refer to Table 6.0.3.

⁴ Total Exposure = Avg Food & Water Exposure + Residential Exposure).

⁵ Aggregate MOE = [NOAEL/ (Avg Food & Water Exposure + Residential Exposure)].

7.3 Intermediate-Term Aggregate Risk

There are no residential use scenarios that will result in potential intermediate term exposure to difenoconazole. Therefore, an intermediate-term aggregate was not performed.

7.4 Summary Findings of Separate Aggregate Assessment for Triazole Metabolites

Application of difenoconazole also results in potential exposures to the triazole metabolites: 1,2,4-triazole (T), triazolylalanine (TA) and triazolylacetic acid (TAA). These compounds are considered to be toxicologically different from difenoconazole. HED recently conducted a separate aggregate risk assessment for these compounds with the resulting exposure estimates less than HED's level of concern (D436745, T. Morton, 11/15/2016).

8.0 CUMULATIVE EXPOSURE/RISK CHARACTERIZATION

Difenoconazole is a member of the conazole class of fungicides containing the 1,2,4-triazole moiety. Although conazoles act similarly in plants (fungi) by inhibiting ergosterol biosynthesis, there is not necessarily a relationship between their pesticidal activity and their mechanism of toxicity in mammals. Structural similarities do not constitute a common mechanism of toxicity. Evidence is needed to establish that the chemicals operate by the same, or essentially the same, sequence of major biochemical events (EPA, 2002). In conazoles, however, a variable pattern of toxicological responses is found; some are hepatotoxic and hepatocarcinogenic in mice. Some induce thyroid tumors in rats. Some induce developmental, reproductive, and neurological effects in rodents. Furthermore, the conazoles produce a diverse range of biochemical events including altered cholesterol levels, stress responses, and altered DNA methylation. It is not clearly understood whether these biochemical events are directly connected to their toxicological outcomes. Thus, there is currently no evidence to indicate that conazoles share common mechanisms of toxicity and EPA is not following a cumulative risk approach based on a common mechanism of toxicity for the conazoles. For information regarding EPA's procedures for cumulating effects from substances found to have a common mechanism of toxicity, see EPA's website at <http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/cumulative-assessment-risk-pesticides>.

This class of compounds can form the common metabolite 1,2,4-triazole and two triazole conjugates (triazolylalanine and triazolylacetic acid). To support existing tolerances and to establish new tolerances for triazole-containing pesticides, including difenoconazole, EPA conducted a human health risk assessment for exposure to 1,2,4-triazole, triazolylalanine, and triazolylacetic acid resulting from the use of all current and pending uses of any triazole-containing fungicide. The risk assessment is a highly conservative, screening-level evaluation in terms of hazards associated with common metabolites (e.g., use of a maximum combination of uncertainty factors) and potential dietary and non-dietary exposures (*i.e.*, high end estimates of both dietary and non-dietary exposures). The Agency retained a 3X for the LOAEL to NOAEL safety factor when the reproduction study was used. In addition, the Agency retained a 10X for the lack of studies including a developmental neurotoxicity (DNT) study. The assessment includes evaluations of risks for various subgroups, including those comprised of infants and children. The Agency's complete risk assessment is found in the propiconazole reregistration docket at <http://www.regulations.gov>, Docket Identification (ID) Number EPA-HQ-OPP-2005-0497. The Agency's latest updated aggregate risk assessment for the triazole-containing metabolites was finalized on November 15, 2016 (D436745) and includes the proposed new uses of difenoconazole.

9.0 OCCUPATIONAL EXPOSURE/RISK CHARACTERIZATION

Occupational handler and post-application exposure scenarios have been identified for the proposed uses of difenoconazole on cotton, rice and wild rice. Based on the product labels and information provided by the registrant, short- and intermediate-term exposure is expected for occupational handlers and post-application activities. Chronic exposure is not expected for the proposed use patterns.

9.1 Occupational Handler Exposure and Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event. There is a potential for short- and intermediate-term exposures to difenoconazole during mixing, loading, and application activities through the dermal and inhalation routes.

Occupational handler exposure and risk estimates for the proposed new foliar uses on cotton, rice and wild rice are all expected to result in comparable exposure scenarios to those previously assessed for use on canola and oilseed subgroup 20A (D412811, I. Nieves, 11/13/2013) and as discussed in a recent risk assessment for this chemical (D421188, I. Nieves, 2/24/2015). The application rates and methods proposed for these new uses (cotton, 0.115 lb ai/A; and rice and wild rice, 0.123 lb ai/A) are similar to the ones previously assessed (0.113 lb ai/A), and risk estimates were quantified at similar amounts used for application to high acreage crops. No risk estimates of concern were identified for any of the previous uses utilizing label required PPE (*i.e.*, long shirt, long pants, shoes, socks and gloves). Based on the premise that all uses require

the same PPE previously labeled, and there have been no revisions to the toxicological database/endpoints and/or to the occupational methods used since the date of the recent assessment, all proposed new uses are not of concern to the Agency.

9.2 Occupational Post-Application Exposure and Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

Dermal Exposure

Post-application dermal exposure and risk estimates for the proposed new uses are all expected to result in comparable/identical exposure scenarios to those previously assessed for use on canola and oilseed subgroup 20A (D412811, I. Nieves, 11/13/2013) and as discussed in a recent risk assessment for this chemical (D421188, I. Nieves, 2/24/2015). The application rates and methods proposed for these new uses (cotton, 0.115 lb ai/A; and rice and wild rice, 0.123 lb ai/A) are similar to the ones previously assessed (0.113 lb ai/A). No risk estimates of concern were identified for any of the previous uses for any reentry activities assessed. Based on the premise that no new dislodgeable foliar residue (DFR) studies have been submitted, and there have been no revisions to the toxicological database/endpoints and/or to the occupational post-application SOPs since the date of the recent assessment, all post-applications activities related to the proposed new uses would not result in greater risks than those assessed for the canola and oilseed subgroup 20A previously and, therefore, are deemed not of concern to the Agency.

Inhalation Exposure

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (<http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037>). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (<http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219>). During Registration Review, the Agency will utilize this analysis to determine if data (*i.e.*, flux studies, route-specific inhalation toxicological studies) or further analysis is required for difenoconazole.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the

Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency risk assessments.

9.2.1 Restricted Entry Interval

The REI specified on the proposed label is based on the acute toxicity of difenoconazole. Difenoconazole is classified as Toxicity Category III for acute dermal toxicity and eye irritation, and Toxicity Category IV for skin irritation potential. It is not a skin sensitizer. Short- and intermediate-term post-application risk estimates were not a concern on day 0 (12 hours following application) for all post-application activities. Under 40 CFR 156.208 (c) (2) (iii), active ingredients classified as Acute III or IV for acute dermal, eye irritation and primary skin irritation are assigned a 12-hour REI. Therefore, the [156 subpart K] Worker Protection Statement interim REI of 12 hours on the proposed labels is adequate to protect agricultural workers from post-application exposures to difenoconazole.

10. REFERENCES

Difenoconazole (128847) Screening Level Usage Analysis (SLUA) May 09, 2016

Difenoconazole. Human Health Risk Assessment for Proposed New Foliar Uses on legume subgroup 6C and bushberry subgroup 13-07B; post-harvest uses on pome fruit group 11-10; and ornamental plants and vegetable transplants grown in both indoor and outdoor production facilities. – I. Nieves; D422992, D421429, D421216, D421201, D421208, D421188, and D413471; 2/24/2015.

Difenoconazole. New Foliar Uses on Cottonseed Subgroup 20C, Rice and Wild Rice. Summary of Analytical Chemistry and Residue Data. - B. Cropp-Kohlligian; D434958; 9/7/2016.

Difenoconazole. Acute and Chronic Aggregate Dietary Exposure and Risk Assessments for the Petition for Use of Difenoconazole on Globe Artichoke, Ginseng and Greenhouse Grown Cucumbers and Conversion of the Established Foliar Uses/Tolerances for Stone Fruit and Tree Nut Crop Groups to Fruit, Stone, Group 12-12 and the Nut, Tree, Group 14-12. - T. Morton; D426491; 7/1/2015.

Difenoconazole. Acute and Chronic Aggregate Dietary Exposure and Risk Assessments for the Petition for Use of Difenoconazole on Cottonseed Subgroup 20C, Rice and Wild Rice. - T. Morton; D434959; 3/15/2017.

Drinking Water Exposure Assessment in Support of the New Use Registration of Multiple Difenoconazole Formulated Products on Artichoke, Berry Bushberry Subgroup 13-07B, Ginseng, and Bean and Pea, Dried Shelled (except Soybean) Subgroup 6C as well as Conversion of Stone Fruit Crop Group 12-12 and Tree Nuts Crop Group 14-12. – F. Khan; D421092; 11/13/2014.

Drinking Water Exposure Assessment in Support of Proposed New Uses on Cotton, Cotton Seed (subgroup 20C), Rice and Wild Rice. – F. Khan; D432384; 10/5/2016.

Difenoconazole. Occupational and Residential Exposure Assessment for a Proposed Use on Canola and Oilseed Subgroup 20A. - I. Nieves; D412811; 9/13/2013.

Difenoconazole. Occupational and Residential Exposure Assessment to Evaluate the Risk from Proposed Uses on Post-Harvest Potatoes, and the Expansion of Various Crop Groups Including: Citrus Fruit Group 10-10; Fruiting Vegetable Subgroups 8-10; Low Growing Berry Subgroup 13-07G, except cranberry; Pome Fruit, Crop Group 11-10 and Fruiting Vegetable, Crop Group 8-10). - I. Nieves; D398608; 5/30/2012.

Difenoconazole. Occupational and Residential Exposure Assessment for the Proposed New Use of Difenoconazole on Strawberry, Carrot, Chickpeas, Soybean, Stone Fruit: Group 12 and Golf Course Turfgrass. – R. Daiss; D371037; 2/24/2011.

Difenoconazole. Occupational and Residential Exposure/Risk Assessment for the Proposed New Uses of Difenoconazole on Fruiting Vegetables, Tuberous and Corm Vegetables, Pome Fruit, Sugar Beets and Ornamentals - Mark I. Dow; D340044; 7/27/2007.

Common Triazole Metabolites: Updated Dietary (Food + Water) Exposure and Risk Assessment to Address The New Section 3 Registrations For Use of Difenoconazole on Rice and Cotton. - T. Morton; D435630; 11/2/2016.

Common Triazole Metabolites: Updated Aggregate Human Health Risk Assessment to Address The New Section 3 Registrations For Use of Difenoconazole on Rice and Cotton. – T. Morton; D436745; 11/15/2016.

APPENDIX A. TOXICOLOGY DATA SUMMARY

A.1 Guideline Data Requirements - Difenoconazole

Guideline No.	Study Type	Technical		MRID No.
		Required	Submitted	
870.3100	Subchronic (Oral) Toxicity - Rodent	Y	Y	42090022
870.3150	Subchronic (Oral) Toxicity - Non-Rodent	Y	Y	42090021
870.3200	21/28-Day Dermal Toxicity	N	Y	42090013
870.3250	90-Day Dermal Toxicity	N	N	42090013
870.3465	90-Day Inhalation Toxicity	N*	N	46950310
870.3700a	Prenatal Developmental Toxicity - Rodent	Y	Y	42090016
870.3700b	Prenatal Developmental Toxicity - Non-Rodent	Y	Y	42710008
870.3800	Reproduction and Fertility Effects	Y	Y	42090017
870.4100a	Chronic (Oral) Toxicity - Rodent	Y	Y	42710008
870.4100b	Chronic (Oral) Toxicity - Non-Rodent (Dog)	Y	Y	42090012
870.4200a	Carcinogenicity - Rat	Y	Y	42710005
870.4200b	Carcinogenicity - Mouse	Y	Y	42090019
870.4300	Combined Chronic Toxicity /Carcinogenicity	Y	Y	42710010
870.6100a	Neurotoxicity - Acute Delayed Neurotox. - Hen	N	N	42090015
870.6100b	Neurotoxicity - Subchronic - Hen	N	N	42710006
870.6200a	Neurotoxicity - Acute - Rat	Y	Y	42090012
870.6200b	Neurotoxicity -Subchronic - Rat	Y	Y	42710005
870.6300	Developmental Neurotoxicity	N	N	42090019
870.7485	General Metabolism	Y	Y	42710010
870.7600	Dermal Penetration	Y	Y	42090015
870.7800	Immunotoxicity	Y	Y	42710006

* The Hazard and Science Policy Council (HASPOC) concluded that a 28-day inhalation toxicity study is not required at this time (TXR 0054074).

A.2 Toxicity Profiles

Table A.1. Acute Toxicity Profile – Difenoconazole				
Guideline No.	Study Type	MRID No.	Results	Toxicity Category
870.1100	Acute oral	42090006	LD ₅₀ = 1450 mg/kg	III
870.1200	Acute dermal	42090007	LD ₅₀ > 2010 mg/kg	III
870.1300	Acute inhalation	42090008	LC ₅₀ > 3.3 mg/L	III
870.2400	Eye irritation	42090009	Mild irritation reversible in 7 days	III
870.2500	Dermal irritation	40789807	Slight irritation	IV
870.2600	Skin sensitization	42090011, 42710004	Negative	N/A

Table A.2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100	90-Day oral toxicity (rat)	42090022 (1987) Acceptable/guideline 0, 20, 200, 750, 1500 or 3000 ppm 0, 1, 10, 37.5, 75 and 150 mg/kg/d	NOAEL = 20 ppm (1 mg/kg/day) LOAEL = 200 ppm (10 mg/kg/day) based on the 10% decrease in body weight in the 200 ppm females (as well as a negative trend in feed consumption) and Increases in absolute liver weights in both sexes
870.3100	90-Day oral toxicity (mouse)	42090021 (1987) Acceptable/guideline 0, 20, 200, 2500, 7500 or 15,000 ppm M: 0, 2.9, 30.8, 383.6, 1125 and 2250 mg/kg/d F: 0, 4.1, 41.5, 558.9, 1125 and 2250 mg/kg/d	NOAEL = 20 ppm (2.9 mg/kg/day) LOAEL = 200 ppm (30.8 mg/kg/day) based on body weight changes & liver histopathology.
870.3150	26-Week oral toxicity	42090012 (1987) Acceptable / guideline 0, 100, 1000, 3000 or 6000 ppm M: 0, 3.6, 31.3, 96.6 and 157.8 mg/kg/d F: 0, 3.4, 34.8, 110.6 and 203.7 mg/kg/d	NOAEL = 3000 ppm (31.3 mg/kg/day in males/34.8 mg/kg/day in females) LOAEL = 6000 ppm (96.6 mg/kg/day in males/110.6 mg/kg/day in females), based primarily on microscopic examination of CGA 169374-related lenticular cataracts.
870.3200	21/28-Day dermal toxicity (rat)	42090013 (1987) Acceptable / guideline 0, 10, 100 and 1000 mg/kg/d	NOAEL = 10 mg/kg/day LOAEL = 100 mg/kg/day based on statistically significant decrements in body weight, body weight gain, and food consumption.
870.3200	21/28-Day dermal toxicity (rat)	46950310 (2000) Acceptable/ guideline 0, 10, 100 and 1000 mg/kg/d	NOAEL (systemic) = 1000 mg/kg/day LOAEL (systemic) was not determined. NOAEL (dermal) = 100 mg/kg/day LOAEL (dermal) = 1000 mg/kg/day based on hyperkeratosis at the skin application site.

Table A.2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3700a	Prenatal developmental in (rat)	42090016, 42710007 (1987) Acceptable / guideline 0, 2, 20, 100 or 200 mg/kg/d from GD 6-15 (nominal doses differed widely from theoretical, this required altering NOAEL/LOAEL values)	Maternal NOAEL = 16 mg/kg/day LOAEL = 85 mg/kg/day based on decreased body weight gain (-24%) and food consumption and excessive salivation and a slightly higher incidence of red vaginal exudate. At 171 mg/kg/day, these effects were more pronounced. Developmental NOAEL = 85 mg/kg/day LOAEL = 171 mg/kg/day based on alterations in fetal ossification. The incidence of bifid or unilateral ossification of the thoracic vertebrae was significantly increased on the fetal basis. There were also significant increases in the average number of ossified hyoid and decreases in the average number of sternal centers of ossification (per fetus per litter). The average number of ribs was significantly increased (with accompanying increases in the number of thoracic vertebrae), and decreases in the number of lumbar vertebrae. These findings may be related to maternal toxicity.
870.3700b	Prenatal developmental in (rabbit)	42090017, 42710008 (1987) Acceptable / guideline 0, 1, 25 or 75 mg/kg/d from GD 7-19; 19 rabbits/dose	Maternal NOAEL = 25 mg/kg/day LOAEL = 75 mg/kg/day based on decreased body weight gain and food consumption, death of one rabbit (due to “apparent treatment-related anorexia”) and abortion in two rabbits. Developmental NOAEL = 25 mg/kg/day LOAEL = 75 mg/kg/day based on non-significant increases in post-implantation loss and resorptions/doe and a significant decrease in fetal weight.
870.3800	Reproduction and fertility effects (rat)	42090018 (1988) Acceptable / guideline 0, 25, 250 or 2500 ppm 0, 1.25, 12.5 and 125 mg/kg/d	Parental/Systemic NOAEL = 25 ppm (1.25 mg/kg/day) LOAEL = 250 ppm (12.5 mg/kg/day) based on reductions (statistically non-significant) in body weight gain which appear to be part of a dose-related trend days 70-77 prior to mating, days 0-7 of gestation, and days 7-14 of lactation (-17% to -42% compared to controls). Offspring NOAEL = 25 ppm (1.25 mg/kg/day) LOAEL = 250 ppm (12.5 mg/kg/day) based on a significant reduction in the body weight of F1 male pups on day 21 (-7%).
870.4100b	Chronic toxicity (dog)	42090012, 42710005 (1988) Acceptable / guideline 0, 20, 100, 500 or 1500 ppm M: 0, 0.71, 3.4, 16.4 and 51.2 mg/kg/d F: 0, 0.63, 3.7, 19.4 and 44.3 mg/kg/d	NOAEL = 100 ppm (3.4 mg/kg/day in males/3.7 mg/kg/day in females) LOAEL = 500 ppm (16.4 mg/kg/day in males/19.4 mg/kg/day in females), based on significant inhibition of body weight gain in females.
870.4200	Carcinogenicity (rat)	42090019, 42710010 (1989) Acceptable / guideline 0, 10, 20, 500 or 2500 ppm M: 0, 0.48, 0.96, 24.12 and 123.7 mg/kg/d F: 0, 0.64, 1.27, 32.79 and 169.6 mg/kg/d	NOAEL = 20 ppm (0.96 mg/kg/day in males/1.27 mg/kg/day in females) LOAEL = 500 ppm (24.1/32.8 mg/kg/day (M/F)) based on cumulative decreases in body-weight gains (-6 to -11% of the controls). No evidence of carcinogenicity

Table A.2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.4300	Carcinogenicity (mouse)	42090015, 42710006 (1989) Acceptable / guideline 0, 10, 30, 300, 2500 or 3000 ppm M: 0, 1.51, 4.65, 46.29, 423.1 and 818.9 mg/kg/d F: 0, 1.9, 5.63, 57.79 and 512.6 mg/kg/d	NOAEL = 30 ppm (4.7 mg/kg/day in males/5.6 mg/kg/day in females) LOAEL = 300 ppm (46.3 mg/kg/day in males/57.8 mg/kg/day in females) based on reductions in the cumulative body weight gains and hepatocellular hypertrophy, liver necrosis, fatty changes in the liver and bile stasis in the 300, 2500 & 4500 ppm groups. Evidence of carcinogenicity (liver adenoma/carcinoma in both sexes)
870.5100	<i>In vitro</i> bacterial gene mutation (<i>Salmonella typhimurium</i> / <i>E. coli</i>) / mammalian activation gene mutation assay	42090019, 42710010 (1989) Acceptable / guideline 340 - 5447 µg/plate; 85 - 1362 µg/plate (repeat assay with TA1537 and TA98)	There were sufficient and valid data to conclude that CGA 169374 technical was negative in the microbial gene mutation assay.
870.5300	<i>in vitro</i> mammalian cell gene mutation assay in mouse lymphoma cells	42090024 (1986) Unacceptable/ guideline	No conclusion can be reached from the three non-activated and two S9 activated mouse lymphoma forward mutation assays conducted with difenoconazole technical. The study was seriously compromised.
870.5375	<i>In vitro</i> Mammalian Cytogenetics (chromosomal aberrations) assay in Chinese hamster CHO cells	46950319 (2001) Acceptable/ guideline 0, 21.99, 27.49, or 34.36 µg/mL (-S9) 0, 34.36, 53.69 or 67.11 µg/mL (+S9)	There was evidence of a weak induction of structural chromosomal aberrations over background in the presence of S9-mix.
870.5375	<i>In vitro</i> Mammalian Cytogenetics (chromosomal aberrations) assay in Chinese hamster CHO cells	46950321 (2001) Acceptable/ guideline 0, 26.3, 39.5 or 59.3 µg/mL (-S9) 0, 11.7 or 17.6 µg/mL (+S9)	There was evidence of a weak induction of structural chromosomal aberrations over background.
870.5375	<i>In vitro</i> Mammalian Cytogenetics (chromosomal aberrations) assay in human lymphocytes	46950323 (2001) Acceptable/ guideline 0, 5, 30 or 75 µg/mL (-S9) 0, 5, 30 or 62 µg/mL (+S9)	There was no evidence of structural chromosomal aberrations induced over background.
870.5385	<i>In vivo</i> mammalian chromosomal aberration test Assay in Mice	42090023 (1986) Unacceptable/guideline 250, 500 or 1000 mg/kg	There was no evidence of a cytotoxic effect on the target organ or significant increase in the frequency of nuclear anomalies (micronuclei). However, the study was compromised.

Table A.2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.5395	<i>In vivo</i> mammalian cytogenetics - erythrocyte micronucleus assay in mice	41710011 (1992) Acceptable/guideline Doses up to 1600 mg/kg	Mice bone marrow - No increase in micronucleated polychromatic erythrocytes occurred with CGA-1 69374 (91.2% ai).
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	4210012 (1992) Acceptable/ guideline Doses up to 50 µg/mL	CGA-i69374 tech. (92.2% ai) was considered to be negative in the unscheduled DNA synthesis assay in rat primary hepatocytes as measured by an autoradiographic method at concentrations up to 50.0 µg/mL.
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	42090027 (1985) Unacceptable/ guideline 0.25-31.25 µg/mL	No conclusion can be reached from the unscheduled DNA synthesis (UDS) primary rat hepatocyte assay conducted with difenoconazole technical at concentrations ranging from 0.25 to 31.25 µg/mL. The sensitivity of the study was severely compromised.
870.5550	Unscheduled DNA Synthesis in Mammalian Cells in Culture	42090026 (1985) Unacceptable/ guideline 0.08-10 µg/mL	No conclusion can be reached from the unscheduled DNA synthesis (UDS) human fibroblast assay conducted with difenoconazole tech. at conc. ranging from 0.08 to 10 µg/mL.
870.6200a	Acute neurotoxicity screening battery	46950327 (2006) Acceptable/ guideline 0, 25, 200 or 2000 mg/kg/d	NOAEL (M) = 25 mg/kg/day LOAEL (M) = 200 mg/kg/day based on reduced fore-limb grip strength in males on day 1 and increased motor activity on Day 1. No histologic findings. NOAEL (F) = 200 mg/kg/day LOAEL (F) = 2000 mg/kg/day based on decreased body weight, the following clinical signs: upward curvature of the spine, tip-toe gait, decreased activity, piloerection and sides pinched in and decreased motor activity. No histologic findings.
870.6200b	Subchronic neurotoxicity screening battery	46950329 (2006) Acceptable/ guideline 0, 40, 250, or 1500 ppm M; 0, 2.8, 17.3 or 107.0 mg/kg/d F: 0, 3.2, 19.5, or 120.2 mg/kg/d	NOAEL (M) = 40 ppm (2.8 mg/kg/day) LOAEL (M) = 250 ppm (17.3 mg/kg/day) based on decreased hind limb strength. No histologic findings. NOAEL (F) = 250 ppm (19.5 mg/kg/day) LOAEL (F) = 1500 (120.2 mg/kg/day) based on decreased body weight, body weight gain and food efficiency. No histologic findings.
870.7800	Immunotoxicity [dietary] - Mouse	48696701 (2011) Acceptable/ guideline 0, 20, 200, 1000, or 1500 pm (0, 3, 35, 177, or 247 mg/kg/day) for 28 days.	Systemic toxicity NOAEL = 200 ppm (35 mg/kg/day) Systemic toxicity LOAEL = 1000 ppm (177 mg/kg/day) based on decreased body weight gains and liver toxicity Immunotoxicity NOAEL = 200 ppm (35 mg/kg/day) Immunotoxicity LOAEL = 1000 ppm (177 mg/kg/day) based on decreased mean anti-SRBC IgM levels.
870.7600 Dermal Penetration	<i>In vivo</i> Dermal Penetration in the Rat, <i>In vitro</i>	47453201 (2007)	See TXR 0056473
870.7600 Dermal Penetration	<i>In vivo</i> Dermal Penetration in the Rat,	46950333 (2003)	See TXR 0056473

Table A.2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.7600 Dermal Penetration	<i>In vitro</i> Absorption through Human Epidermis;	47453202 (2007)	See TXR 0056473
870.7600 Dermal Penetration	<i>In vitro</i> Absorption through Rat Epidermis;	47453203 (2007)	See TXR 0056473
870.7485	Metabolism and pharmacokinetics (rat)	42090028 (1990) Acceptable/ guideline 14 daily doses of 0.5 or 300 mg/kg	Male and female Sprague-Dawley rats. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg [¹⁴ C]CGA-169374, or 0.5 mg/kg unlabeled GGA-169374 by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [¹⁴ C]CGA-169374 on day 15. The test compound was labeled with C ¹⁴ at either the phenyl or triazole ring.
870.7485	Metabolism and pharmacokinetics (rat)	42090028 (1990) 42090029 (1987) 42090030 (1987) 42090031 (1988) Acceptable/ guideline Single oral dose 0.5 or 300 mg/kg 14 daily doses of 0.5 or 300 mg/kg	Male and female Sprague-Dawley rats. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg [¹⁴ C]CGA-169374, or 0.5 mg/kg unlabeled GGA-169374 by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [¹⁴ C]CGA-169374 on day 15. The test compound was labeled with C ¹⁴ at either the phenyl or triazole ring. [¹⁴ C] CCA 169374 was rapidly and extensively distributed, metabolized, and excreted in rats for all dosing regimens. The metabolism of difenoconazole appears to be extensive because the metabolites accounted for most of the recovered radioactivity in the excreta. Three major metabolites were identified in the feces (<i>i.e.</i> metabolites A, B, and C). Two of the metabolites were separated into isomers (<i>i.e.</i> , A1, A2, B1, and B2). Metabolite C was detected only in the high-dose groups, indicating that metabolism of difenoconazole is dose-related and involves saturation of the metabolic pathway. Free triazole metabolite was detected in the urine of triazole-labeled groups and its byproduct was detected in the liver of phenyl labeled groups only. Other urinary metabolites were not characterized.

870.7485	Metabolism and pharmacokinetics (rat)	<p>42090028 (1990) 42090029 (1987) 42090030 (1987) 42090031 (1988)</p> <p>Acceptable/ guideline in conjunction with MRIDs 420710013, 42710014</p> <p>Single oral dose 0.5 or 300 mg/kg 14 daily doses of 0.5 or 300 mg/kg</p>	<p>The absorption, distribution, metabolism, and excretion of CGA 169374 were studied in groups of male and female Sprague-Dawley rats. Animals were administered a single oral gavage dose of 0.5 or 300 mg/kg [¹⁴C]CGA-169374, or 0.5 mg/kg unlabeled GGA-169374 by gavage for 14 days followed by a single gavage dose of 0.5 mg/kg [¹⁴C]CGA-169374 on day 15. The test compound was labeled with C¹⁴ at either the phenyl or triazole ring.</p> <p>[¹⁴C] CCA 169374 was rapidly and extensively distributed, metabolized, and excreted in rats for all dosing regimens. The extent of absorption is undetermined pending determination of the extent of biliary excretion. The 4-day recoveries were 97.94-107.75% of the administered dose for all dosing groups. The elimination of radioactivity in the feces (78.06-94.61% of administered dose) and urine (8.48-21.86%) were almost comparable for all oral dose groups, with slightly higher radioactivity found in the feces of the high-dose group than the low-dose groups. This was probably due to biliary excretion, poor absorption or saturation of the metabolic pathway. The radioactivity in the blood peaked at about 24-48 hours. Half-lives of elimination appear to be approximately 20 hours for the low-dose groups and 33-48 hours for the high-dose group. The study results also indicate that difenoconazole and/or its metabolites do not bioaccumulate to an appreciable extent following oral exposure since all the tissues contained negligible levels (< 1%) of radioactivity 7 days post exposure.</p> <p>The metabolism of difenoconazole appears to be extensive because the metabolites accounted for most of the recovered radioactivity in the excreta. Three major metabolites were identified in the feces (<i>i.e.</i> metabolites A, B, and C). Two of the metabolites were separated into isomers (<i>i.e.</i>, A1, A2, B1, and B2). Metabolite C was detected only in the high-dose groups, indicating that metabolism of difenoconazole is dose-related and involves saturation of the metabolic pathway. Free triazole metabolite was detected in the urine of triazole-labeled groups and its byproduct was detected in the liver of phenyl labeled groups only. Other urinary metabolites were not characterized.</p> <p>These studies indicate that distribution, metabolism, and elimination of CGA-169374 were not sex related. There was a slight dose difference in the metabolism and elimination of CGA-169374. In phenyl and triazole labeling studies, fecal excretion of radioactivity was higher in the high dose animals compared to the low dose animals, and an additional metabolite was found in the feces of the high dose animals compared to the low dose animals. There was no major difference in the distribution and excretion of radioactivity with labeling at the phenyl and triazole ring positions, however, there were some</p>
----------	---------------------------------------	--	---

Table A.2. Subchronic, Chronic and Other Toxicity Profile of Difenoconazole			
Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
			different metabolites identified. The studies also showed that administration of 0.5 and 300 mg/kg CGA- 169314 did not induce any treatment related clinical effects.

A.3 Toxicological Endpoints

A.3.1 Acute Population Adjusted Doses (aPAD) – All Populations

Selected Study: Acute Neurotoxicity Study in Rats

MRID 46950327

Dose and Endpoint for Establishing an aPAD: NOAEL is 25 mg/kg/day. LOAEL is 200 mg/kg/day based on reduced fore-limb grip strength in males on day 1.

Uncertainty Factor (UF): 100, this includes 10x for interspecies extrapolation and 10x for intraspecies variation, 1X FQPA SF.

Comments about Study/Endpoint: The selected endpoint is considered appropriate for acute dietary exposure because effects were seen after a single dose. The endpoint is protective of the general population and all subpopulations for effects seen in the acute neurotoxicity study in rats. It is also protective of developmental and maternal effects observed in the rabbit developmental toxicity study at the LOAEL of 75 mg/kg/day and NOAEL of 25 mg/kg/day.

$$aRfD \text{ (General Population)} = \frac{25 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}} = 0.25 \text{ mg/kg}$$

A.3.2 Chronic Population Adjusted Dose (cPAD) – All Populations

Selected Study: Chronic/Oncogenicity Study in Rats

MRID 42090019/20

Dose and Endpoint for establishing an cPAD: The NOAEL is 0.96 mg/kg/day. The LOAEL is 24.12 mg/kg/day based on cumulative decreases in body weight gains at 24.12 mg/kg/day in males.

$$cRfD \text{ (General Population)} = \frac{0.96 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}} = 0.01 \text{ mg/kg}$$

Uncertainty Factor (UF): 100: This includes 10X for interspecies extrapolation, 10x for intraspecies variation, 1X FQPA SF.

A.3.3 Incidental Oral Exposure (Short-Term)

Selected Study: Two Generation Reproduction Study in Rats

MRID 42090018

Dose and Endpoint for Establishing POD: The NOAEL is 1.25 mg/kg/day based on decreased pup weight in males at 12.5 mg/kg/day (LOAEL) on day 21, and reductions in body weight gain in F0 females.

Uncertainty Factor (UF): An MOE 100 is required for the short- and intermediate-term scenarios for dermal exposure is based on the conventional uncertainty factor of 100. This includes 10x for interspecies extrapolation and 10x for intraspecies variation.

Comments about Study/Endpoint: There are no residential uses for difenoconazole that would result in incidental oral exposure to children. However, a short term oral exposure endpoint is required for aggregate risk assessment.

A.3.4 Dermal Absorption

A dermal absorption factor (DAF) is applied when dermal exposure endpoints are selected from oral toxicity studies. The dermal factor converts the oral dose to an equivalent dermal dose for the risk assessment. A DAF of 6% was selected for use in risk assessment based on available in vivo dermal absorption studies in rat and in vitro dermal absorption studies conducted with rat and human skin (TXR 0056473).

A.3.5 Dermal Exposure (Short and Intermediate-Term)

Selected Study: Two Generation Reproduction Study in Rats (MRID 42090018)

Dose and Endpoint for Establishing POD: The NOAEL is 1.25 mg/kg/day based on decreased pup weight in males at 12.5 mg/kg/day (LOAEL) on day 21 and reductions in body weight gain in F0 females. Dermal absorption is 6%.

Uncertainty Factor (UF): An MOE 100 is required for the short- and intermediate-term scenarios for dermal exposure is based on the conventional uncertainty factor of 100. This includes 10x for interspecies extrapolation and 10x for intraspecies variation.

Comments about Study/Endpoint: Although dermal toxicity studies are available, a POD from an oral study was selected because effects in young animals (decreased pup weight) the primary effect of concern for short, intermediate and long term exposure is not specifically evaluated in the available dermal toxicity studies that only assess adult animals. The selected endpoint is protective of offspring effects from dermal exposure. A DAF of 6% is applied to the POD for dermal exposure.

A.3.6 Inhalation Exposure (Short- and Intermediate-Term)

Selected Study: Two Generation Reproduction Study in Rats (MRID 42090018)

APPENDIX B. PHYSICAL/CHEMICAL PROPERTIES

Physicochemical Properties of Difenoconazole.		
Parameter	Value	Reference
Melting point	78.6 °C	DP#s 172067 and 178394, 10/26/92, R. Lascola
pH	6-8 at 20 °C (saturated solution)	
Density	1.37 g/cm ³ at 20 °C	
Water solubility	3.3 ppm at 20 °C	
Solvent solubility	<u>g/100 mL at 25 °C:</u> n-hexane: 0.5 1-octanol: 35 toluene: 77 acetone: 88 ethanol: 89	
Vapor pressure	2.5 x 10 ⁻¹⁰ mm Hg at 25 °C	
Dissociation constant, pK _a	pure grade (99.3% ± 0.3%) difenoconazole in water (with 4% methanol) at 20°C is 1.1	DP# 375159, 5/26/10, B. Cropp-Kohlligian
Octanol/water partition coefficient, Log(K _{ow})	4.2 at 25 °C	DP#s 172067 and 178394, 10/26/92, R. Lascola
UV/visible absorption spectrum	λ _{max} at about 200 and 238 nm (in methanol at 26 °C)	PMRA Proposed Regulatory Decision Document on Difenoconazole, 4/14/99 (PRDD99-01)

APPENDIX C. STUDIES REVIEWED FOR ETHICAL CONDUCT

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies were determined to require a review of their ethical conduct, have received that review and have been determined to be ethical.

The PHED Task Force, 1995. The Pesticide Handlers Exposure Database, Version 1.1. Task Force members Health Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association, released February, 1995.

The Agricultural Handler Exposure Task Force (AHETF), 2011. The Occupational Handler Unit Exposure Surrogate Reference Table. U.S. Environmental Protection Agency. Released June 21, 2011.

Klonne, D. (1999) Integrated Report for Evaluation of Potential Exposures to Homeowners and Professional Lawn Care Operators Mixing, Loading, and Applying Granular and Liquid Pesticides to Residential Lawns: Lab Project Number: OMA005: OMA001: OMA002. Unpublished study prepared by Riceerca, Inc., and Morse Laboratories. 2213 p. (MRID 44972201).

The PHED Task Force, 1995. The Pesticide Handlers Exposure Database, Version 1.1. Task Force members Health Canada, U.S. Environmental Protection Agency, and the National Agricultural Chemicals Association, released February, 199